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CALCIUM AND PHOSPHORUS AND

SMITH,[1] describing the medical treatment of 314 cases of bronchial asthma writes: "When a patient was found to be sensitive, the need for general treatment was explained in detail. The general health of the subject was considered, and he was usually put on a regimen of proper rest and dietary measures, with cod liver oil and calcium lactate in moderate doses."

Novak and Hollander[2] in their study of the serum calcium of 87 patients with hay fever, hyperesthetic rhinitis and the asthmas state that the ionic calcium content of the blood serum is invariably low in hyperesthetic rhinitis and that there are also certain cases of hay fever and asthma which show a low calcium content. Calcium compounds and thyroid extract afforded temporary relief but when combined with vitamin D therapy in the form of ultra-violet irradiation it appeared to have a permanent influence on all of the rhinitis cases and upon approximately 50 per cent of those in the latter two groups.

Sterling[3] writes: "Calcium is beneficial in most hypersensitive cases whether they show a low blood calcium or not. Both calcium and phosphorus help to control the hyperexcitability of the nervous system. . . . While we cannot draw positive conclusions from a study of the above cases, calcium and phosphorus are found of great benefit in the treatment of allergic diseases. This mineral deficiency in asthmatics, hay fever, and allied diseases, whether sensitivity can be proved or not, may be the missing link which makes the allergic differ from the normal. The addition of calcium, phosphorus, and other minerals, for instance, iron, sodium and potassium salts, are possibly responsible for the favorable results in this series of cases."

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Burgess[4] is of the belief that cases of urticaria, especially those showing marked dermographism, and eczema in the vast majority of instances present a marked diminution of precipitable serum calcium. He reports that cases of urticaria and eczema were considerably improved by measures to raise the serum calcium.

Kitsuta[5] reports that in his own case he used cod liver oil and yeast for the treatment of hay fever, with beneficial results. He states: "In administering cod liver oil for the cure of hay fever already developed, I think it advisable to take about 4 teaspoonfuls three times daily. . . ."

Jones[6] found 60 per cent of his cases of exudative diathesis improved with calcium medication and parathyroid extract.

Mollison[7] states that 37 per cent of 40 cases of vasomotor rhinitis were cured and 27 per cent improved by calcium compounds and measures to increase calcium absorption.

Von Gordon[8] believes that hay fever and asthma are neuroses based upon a functional disturbance of the vegetative nervous system leading to a sympathetic hypotonia with or without vagotonia, and to a labile equilibrium of the vagus sympathetic nerves which react pathologically to normally inadequate stimuli. He contends also that a decrease in the blood calcium is one of the most important causes of this lability.

Colomb[9] states that from a therapeutic standpoint calcium is valuable for conditions associated with anaphylactic phenomena. He adds, its absorption is regulated by vitamin D.

Hutton[10] states that disturbances of calcium metabolism are likely to be present in urticaria and eczema.

Pottenger[11] thinks that calcium is definitely identified with sympathetic action. He was successful in completely relieving the paroxysms of asthma by means of calcium therapy.

Klare[12] believes that there is a relationship between the exudative diathesis of childhood and calcium deficiency. He therefore finds calcium therapy indicated in recurrent catarrh, bronchial asthma, hay fever, adenopathies and increased susceptibility to acute infections. He believes that calcium has a specific action in decreasing the hyperirritability of the autonomic nervous system.

Downing and Blumenfeld[13] report several cases of acute and chronic urticaria in which calcium therapy was effective.

Schmidt[14] found ultra-violet light of value in his own case and attributed the result partly to the antispasmodic effect of the treatment.

Ochsenius[15] points out that calcium (*Cont'd*)

1-23 Bibliography on request.

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Original Articles

THE PRESERVATION OF REAGIN IN DRIED SERUM*†

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DRYING as a means of preserving the antibodies in convalescent sera, has been in use for some time. These sera maintain their potency for at least two or three years.[1] This study was undertaken with a view to determine whether the skin sensitizing antibody in hay fever serum remains potent in the dried state and whether there is any advantage in keeping it thus.

Method.—Blood was taken from hay fever patients, allowed to clot, and the serum pipetted off and passed through a Berkefeld filter. The serum was evaporated *in vacuo* in a suction chamber to syrupy consistency and then placed in a desiccator over phosphorus pentoxide until completely dry. When scraped up with a spatula, it then forms yellowish kernels, which were kept in vials on ice. Whenever a passive transfer site was to be made, a few kernels of serum were dropped into 2 c.c. of normal saline, shaken until dissolved, and injected into a normal skin site in quantities of 0.05 c.c. or 0.1 c.c. The serum dissolves with difficulty, often leaving a small gummy residue. Other workers have recommended the addition of phenol to the sera to aid in the redissolving. The passive transfer sites were usually tested in forty-eight hours with 0.02 c.c. of a potent ragweed extract, controls being run on the normal skin of the same person, and also on sites made with two of the dried sera from patients who were not sensitive to ragweed. The reactions were recorded on graph paper in the manner previously described.[2]

In December, 1931, sera were taken from five fall hay fever patients. Three of these patients gave good skin reactions to ragweed; the other two did not react and were used as controls. The sera have been tested at intervals for a period of fourteen months. The three potent sera all gave good passive transfers at first. At the end of fourteen months two of the three

*From the Chicago Municipal Tuberculosis Sanitarium.
†Presented before the Chicago Society of Allergy, Feb. 20, 1933.

still gave definitely positive transfers, but had become relatively feeble; the third had become negative.

In July, 1932, sera from three strongly sensitive fall hay fever subjects were taken, mixed, dried, and tested at intervals since. This pooled serum at seven months, continues to give good passive transfer sites. In all, about 100 passive transfers have been performed. No experiments concerning the exact quantitative reagin value of the dry and moist sera were undertaken.

Action of Dried Serum in the Normal Skin.—The redissolved newly dried serum when injected into the normal skin forms a small wheal and flare which fade out in a few hours leaving no visible evidence except the puncture. After about six months of ageing, however, the dried serum begins to cause an inflammatory reaction in the normal skin. This comes on in a few hours and reaches its height in about twenty-four hours and may persist for several days. In some instances it is severe enough to cause superficial vesiculation and necrosis. Sites which show the inflammatory reaction fail to give a positive Prausnitz-Küstner reaction on injection of the ragweed extract. The inflammatory reaction may be avoided by diluting the dried serum further, in which case it will still give a positive Prausnitz-Küstner reaction. The inflammatory reaction was found to occur only in the tuberculin-sensitive skin and seems to be related to the so-called nonspecific tuberculin reactions which have been described with meat extracts and other animal derivatives. It did not occur in the tuberculin-negative skins of four infants tested, nor on adults who failed to react to 1:1000 dilution of tuberculin. Gay and Chant[3] have described an earlier reaction with heated serum.

DISCUSSION

The fact that reagin is capable of withstanding drying is of interest as an addition to knowledge of its characteristics. The quantitative relations of the potency of the dried serum were not studied here, but the preservation of potency for a period of a year makes it probable that the antibody deteriorates more slowly in the dried state. The greater stability may be helpful in experiments which must be prolonged over a period of months. By the use of the dried serum the reagin concentration can be made higher than that of the original serum. This may prove of value in passive transfer experiments with sera of feeble reagin content. In making atopen-reagin mixtures a concentrated mixture can be obtained by adding dried serum to the liquid atopen extract, instead of the usual dilution of both which occurs when two solutions are mixed.

CONCLUSION

Dried serum from hay fever subjects preserves the sensitizing antibody over a considerable period of time.

I am indebted to Mr. Ben Sher, chemist to the Municipal Tuberculosis Sanitarium, for advice and help in preparing the sera.

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2800 MILWAUKEE AVENUE.

THE LATE VACCINE SKIN REACTION*†

WILLIAM S. THOMAS, M.D. AND MAXIMIN D. TOUART, M.D.
NEW YORK, N. Y.

CLINICAL reactions to vaccine inoculations as studied by us during the past twelve years in upward of 15,000 injections, appear to bear a specific relation to that type of hypersensitiveness that is associated with infection. They are thought to be capable of affording aid in diagnosis and treatment. Among the results of the intradermal injection of bacteria and their products, the late vaccine skin reaction has attracted especial attention in recent years. It is proposed herein to define and describe it, to point out its usefulness as a guide in the diagnosis and treatment of bacterial asthma and other disorders of similar nature and to offer evidence that it may be a specific allergic phenomenon.

Published classifications of the types of human hypersensitiveness have not adequately provided for the inclusion of bacteria as etiologic factors. Still less have bacterial skin reactions received the amount of consideration to which they appear to be entitled. In order to make clear our ideas regarding the relationship of bacteria to certain hypersensitive states, we present the subjoined classification which is adapted from a published table by Coca[6] (Table I).

TABLE I

TYPES OF HUMAN HYPERSENSITIVENESS

1. ATOPY, including atopy due to bacteria.
2. BACTERIAL ALLERGY, synonymous with the tuberculin type of hypersensitiveness and designated by some writers as the hypersensitiveness of infection.
3. CONTACT DERMATITIS.
4. SERUM SICKNESS.
5. DRUG IDIOSYNCRASY.

It is the second type of hypersensitiveness shown in Table I whose presence is believed to be revealed by the occurrence of the late vaccine reaction, which is the subject of this paper.

Reactions to common protein skin tests have been of great aid in the management of the better known forms of human hypersensitiveness, and they are universally employed by allergists. Skin tests with bacteria in

*From the Department of Allergy, St. Luke's Hospital and the Department of Applied Immunology, French Hospital, New York City.
†Read before the Society for the Study of Asthma and Allied Conditions, New York, December 10, 1932.

the infective types of hypersensitiveness, on the other hand, have yet to find widespread adoption because bacterial allergy has seemed to many clinicians to be in a class of itself, undiagnosed and obscure.

We, through our work in this field, have been led to believe that von Pirquet's discovery of hypersensitiveness of the tuberculin type has opened a vista of phenomena of a similar nature in relation to germs other than the Koch bacillus. Moreover, it appears that Mantoux' test with tuberculin may be duplicated with the products of other germs and that the resulting skin reactions may also be useful in the diagnosis and therapy of some common disorders associated with infection. Hypersensitiveness, not only to the tubercle bacillus but also to the more commonly encountered germs that exist in or upon the majority of persons—in other words, the so-called hypersensitiveness to infection—is coming to be recognized as a frequently occurring phenomenon.

It is true that von Pirquet[36] recognized the existence of the wheal reaction to inoculation of extract of tubercle bacilli, but he laid no stress upon its significance in diagnosis. Workers who conduct vaccine tests with various commonly encountered germs observe occasionally, immediate (wheal) reactions as well as delayed ones. The early vaccine skin reaction with its wheal, its pseudopods, its surrounding erythema, and its pruritus appears to differ in no wise from common protein reactions to intradermal tests, either in character or in implications. Quite another thing is the later positive vaccine skin reaction. Not only does this reaction require a longer time for its development, but it is independent of the wheal. It has been seen to occur at the sites of faded wheals as well as at places where there have been no wheals.

We find that our researches have received corroboration from a large amount of laboratory work done by others on vaccines, especially as reported in the literature of the last decade. Some of these investigators have used bacterial vaccines while others have employed bacterial extracts. Some workers have classed as positive those skin reactions which would be considered as negative by others. In some laboratories local reactions have been observed and recorded twenty-four hours after injection, while elsewhere reactions have been noted as of two days or perhaps less than twelve hours after inoculation. Seldom have any two groups of workers in this field used similar methods in their investigations. There has been no accepted standard in general use for guidance in reading or evaluating the reactions to vaccine injections either in laboratory animals or in human beings.

In view of the facts stated above it is perhaps but natural that there have been as yet few important deductions drawn from laboratory investigations made recently with bacterial products. Amid all the confusing reports, however, there appears to be discernible the evidence of an interrelation of immunity and hypersensitiveness. One also frequently sees in the literature unmistakable descriptions of the manifestations of bacterial

allergy—the same process to which von Pirquet first applied his coined word "allergy."

Because of the prevailing uncertainty regarding the method of conducting vaccine tests and of evaluating the significance of the resulting reactions, there appears to be a need of uniformity in vaccine methods both in the animal laboratory and in clinical practice. We, accordingly, offer here a tentative definition of the late or tuberculin type of vaccine skin reaction. It is assumed here that the method of Thomas, Famulener and Touart,[32] which need not be described at this time, is used in making the test.

The late positive vaccine skin reaction is a lesion of the skin of a subject after the lapse of forty-eight hours or more, following and at the site of the intradermal injection of 0.01 c.c. of a 1 per cent (by volume) suspension of killed bacteria in normal saline solution.

In order to be classed as positive, such a reaction must exceed in a definite degree, an accompanying control reaction to an injection of an equal amount of a suitable control solution.

A typical late vaccine skin reaction may be described as a lesion of the skin consisting of a central deeply red area 0.3 cm. in diameter, overlying a palpable red nodule of similar breadth and surrounded by a pink zone or areola 1 cm. or more broad, with or without heat and tenderness of the central red area or of the areola as well and with or without other changes or symptoms.

So great is the variation in the testing doses used by investigators that it seems proper to lay emphasis upon the importance of using only a small bulk of material for the purpose of testing. Coca[6] and Grove[20] have shown that nonspecific or pseudoreactions resulting from the intracutaneous method of testing can almost always be avoided if the volume of material injected does not exceed 0.02 c.c. The testing dose used by us is not greater than 0.01 c.c. as a rule. It contains one vaccine unit, according to Famulener's volumetric method of standardization; that is to say, it contains 80,000,000 bacteria when they are of average streptococcus size.[16, 17]

There appears to be no means by which one can foretell the degree of susceptibility of any individual to vaccines; accordingly the above named, arbitrarily fixed testing dose, based upon experience, has been used. Some patients are so sensitive that this amount of dosage produces in them an undesirably severe reaction. Nevertheless, it is suited to the need of the great majority of patients, and were it smaller it would fail to produce any reaction in those individuals who might be but moderately sensitive to the vaccine in question. All vaccine tests made by us have been accompanied by control injections made with the vaccine diluent or with the diluent plus traces of the culture medium or with the broth itself.

The late skin reaction is read by us at the end of twenty-four hours, again at forty-eight hours and during subsequent days should circumstances make it advisable so to do. It is the forty-eight hour phase of the

reaction that appears to be of the most importance. Unless this third day phenomenon be made the basis of the observation, it does not appear to be possible to judge correctly the result of the test. This point is stressed because a review of the literature discloses a variety of opinions as to the proper time at which the late reaction should be read.

Before presenting a detailed analysis of the late skin reaction, it may be proper to describe the setting in which it has been observed; that is to say, the various other clinical reactions which accompany it, together with a brief characterization of each of them. They are named, briefly described, and their possible significance is noted in Table II. We are convinced that the whole clinical picture resulting from each vaccine inoculation (as shown in Table II) should be considered when one is deciding upon the practical application of the skin reactions as guides in the management of any patient's case.

TABLE II

CLINICAL REACTIONS TO INTRADERMAL INJECTIONS OF VACCINES[33]

NAME OF REACTION	DESCRIPTION	SIGNIFICANCE
Early local reaction	Urticarial wheal occurring within ½ hour at injection site	Presence of bacterial atopy
Late local reaction	Macular or papular lesion at injection site, at its height at end of 48 hours	Presence of bacterial allergy
General toxic reaction	Malaise, prostration, fever, etc.	Systemic response to specific or nonspecific toxins
Symptomatic reaction	Onset or increase of original allergic symptoms	Presence of bacterial allergy
Relief reaction	Temporary relief from original allergic symptoms	Presence of bacterial allergy
Focal reaction	Lighting up of symptoms of infection at site from which vaccine organisms were obtained	Harmfulness of focus to patient
Recurrent local reaction	Reappearance of a faded late local reaction	Undetermined*
Negative reaction	Absence of response to vaccine injection	Absence of bacterial atopy or of bacterial allergy; harmlessness of vaccine organisms to their host†

*This reaction, as encountered in experimental animals, is held by Swift and others to be an evidence of the establishment of bacterial allergy.

†Its further immunologic implications are reserved for discussion in a later communication.

The features that may characterize a late positive vaccine skin reaction, as observed by us, are listed in Table III and are described later in detail. Some of these features are objective in nature, some subjective, others

qualitative and still others quantitative in character and significance. All of them appear to be worthy of study, with a view to their use as guides in diagnosis and treatment.

TABLE III

FEATURES OF THE LATE VACCINE SKIN REACTION

1. Nodule	8. Lymphangitis
2. Redness	9. Pruritus
3. Areola	10. Ecchymosis
4. Swelling	11. Pustule
5. Tenderness	12. Eosinophilia
6. Pain	13. Desquamation
7. Heat	14. Pigmentation

It appears that in order to observe and appraise a late reaction properly, mere inspection is not sufficient. Such reactive phenomena as local heat, pruritus, tenderness and the presence of a nodule, palpable, though not elevated above the level of the surrounding skin—these are features not recognizable by the eye, but they are very frequently encountered and are evidently indications that a pathologic process is taking place. In like manner enlarged, tender lymph nodes, malaise, fever, nausea, and the onset or increase of original allergic symptoms following the intradermal injection of vaccine, these too appear worthy of recognition and consideration in order that their meanings may be applied in planning the subsequent treatment of any case in which they may occur.

The employment of vaccine reactions as guides has been described in a previous paper,[33] but it may be proper to note here the fact that while autogenous vaccine administered intracutaneously or closely under the skin has often been seen to bring on or to intensify such original allergic symptoms as asthma, coryza or arthritic pain, such symptomatic reactions (see Table II) have not been observed unless in the presence of a coexisting late skin reaction.

DESCRIPTION OF THE LATE VACCINE SKIN REACTION

In its general character the late skin reaction is not unlike the Schick reaction. It varies in intensity with the susceptibility of the patient to the effects of the organism causing it. If the wheal reaction to a certain vaccine occurs, it continues to follow repeated injections of the same; a late vaccine skin reaction on the other hand, whatever its features may be, tends to become less marked as it follows successive injections of identical amounts of the same vaccine. Any or several of the features of a late vaccine skin reaction as named in Table III have been observed following intradermal vaccine injections in given cases. Those features most frequently encountered have been the nodule with its overlying redness and the areola.

The *nodule*, as observed, has been slightly elevated above the level of the surrounding skin and is more easily felt than seen. It usually appears

within a few hours after the intradermal injection of a vaccine and is fully developed by the end of the second day. It has been seen to exist for several or many days.

Redness overlies the nodule and is of a darker hue than is the *areola* or pink, erythematous zone surrounding the nodule in well marked late vaccine skin reactions. The areola has often been seen with a breadth of from 1 to 3 cm., but at times it has been observed to measure 5 to 10 cm. in diameter. When present, the areola has usually reached its maximum development in forty-eight hours and has faded rapidly thereafter. Its whole surface sometimes has been seen to be slightly raised above the level of the surrounding skin, and when this condition is present it has been recorded as *swelling*. The presence of swelling of the areola is characteristic of an unusually severe reaction and has always been accompanied by other symptoms, particularly heat and tenderness and even pain.

Tenderness to touch or on pressure at the reaction site has been a commonly noted symptom of positive late vaccine reactions. When present it has been usually confined to the area of the nodule but has not infrequently been observed to extend over the whole of an existing areola. Tenderness has been noted as existing for two or three days following inoculations in a large percentage of the positive reactions.

Pain at the reaction site has seldom been severe enough to be a cause of complaint. When present, pain appears to be but an exaggeration of existing tenderness, and it usually disappears by the end of the second day after inoculation.

Heat.—Elevation of surface temperature at and about the injection site has been frequently observed and has varied with the severity of the reaction. Heat, like the symptom of tenderness, may be felt over the nodule only, but it has often been observed to extend over the surface of an existing areola. Rarely has it lasted more than three days.

Lymphangitis is occasionally a feature of a marked vaccine reaction. Its presence is shown by a broad pink line extending up the limb from the areola, with which it is continuous. When lymphangitis is present at a reaction site, it is usually accompanied by swelling and tenderness of the adjacent connected lymph nodes. Such lymphangitis and adenitis have seldom been found to last more than one day.

Pruritus is often noticed by patients during the first and second days of the existence of a strongly positive late vaccine reaction.

Ecchymosis has been rather frequently seen following and at the site of a faded areola. The hue is usually icteric and lasts a few days.

Pustule.—In a small percentage of positive reaction sites there has been present a pustule, developing on the second day and taking the place of a nodule. In rare instances there has been seen a small area of necrosis of the skin at the inoculation site. Cultures have been taken from such pustules many times, but they have always been sterile and hence the pustules have apparently not been due to infection by living germs.

Eosinophilia.—Examinations in a series of vaccine-tested and treated patients have been made by us[34] and have revealed in the great majority of their positive late reaction sites, the presence of an excess in the number of eosinophil cells over those demonstrable in the circulating blood taken from normal sites in the respective patients.

Desquamation has been a rather infrequent feature in our experience. When it has been present, the symptom has developed three or four days or more after inoculation. The desquamation is fine and branny in character and confined to an area less than 1 cm. in breadth at the center of the reaction site.

Pigmentation of the skin at the former site of a central redness has been seen rather rarely. When present, the dark macule has persisted for weeks or months.

RECORDING AND EVALUATING THE LATE SKIN REACTION

If the late vaccine skin reaction is to be used as a guide in selecting vaccines for therapeutic use or in determining dosage, it is evident that there should be available a satisfactory method of evaluating its significance and recording its features both qualitatively and quantitatively.

A simple code has been used by us, in which the initial letters of the names of each of the features of these reactions serve to indicate not only the presence of that feature but also its size or degree of intensity. Thus, a nodule of 0.3 cm. or less in diameter is recorded as N; if larger, as NN or N2. The redness or macule is recorded in a similar manner by using the letter R or RR or R2. An areola 1 cm. broad becomes A in the code, and an additional A is added for the increase of each centimeter in its breadth. Heat, tenderness, etc., are denoted by the letters H, T, etc., respectively, and if more marked, by HH or TT. For example a reaction consisting of a small nodule, redness, heat, and an areola 1 cm. in diameter is recorded as NRHTA. Should the areola be 3 cm. broad, the above reaction would be expressed as NRHTAAA or NRHTA3.

Probably no clinician would hesitate to consider as positive a reaction which at the end of forty-eight hours exhibited at least a nodule, redness, areola and heat. It has been our practice to regard as positive a reaction which, at the end of forty-eight hours after injection exhibits, in addition to whatever symptoms may be present at the control site, more than three of the features named in Table III and described above. Late reactions occurring during the first twenty-four hours but disappearing before the end of the second day after inoculation, have been discarded from consideration as being nonspecific and not clinically helpful. In order to record late vaccine reactions in terms of plus value, in conformity with the current medical practice, each letter which in the code represents the presence and degree of a feature or symptom of the local reaction, is credited with a count of one. The sum of these counts, minus the sum of the features at the site of the control injection and after deducting also three more al-

lowed for a doubtful zone, will equal the plus value of the reaction. According to this method the reaction recorded last above, if accompanied by a red macule at the control site, would be evaluated or appraised as follows:

Vaccine reaction, NRAAAHT: Count	7
Deduct value of the control reaction (R)	1
Balance remaining	6
From this deduct (for doubtful zone)	3
Leaving the plus value of the vaccine reaction	3

DISCUSSION

The importance of the late vaccine skin reaction as a guide in diagnosis and treatment of infective asthma and other conditions has been emphasized elsewhere by us and clinical evidence of its specific character has been offered.[33, 34, 35] There follows here a summary of such evidence with some additional data.

1. Any given individual's reaction to any given organism is constant until modified by repeated injections of it or through infection by it. This statement is true whether the organism be autogenous or heterogenous in origin.

2. The positive late vaccine reaction has frequently been accompanied by a reproduction or increase of the original allergic symptoms in patients with infective asthma, etc. When such a combination of symptoms, both local* and distant,* is encountered, it may be repeated at will. The repeated occurrence of original symptoms following intradermal injections has not been observed in connection with a negative skin reaction. This association of phenomena is of interest because of the question which has been raised regarding the relationship between bacterial allergy as disclosed by a positive vaccine skin reaction and the symptoms with which the patient may be suffering. Does the occurrence of a positive skin reaction to an autogenous vaccine prove that the organism in question is a cause of the patient's symptoms? Taken alone, it does not do so. The skin reaction merely indicates the presence of an allergic state, specific for the organism in question. In clinical practice it has been customary in such cases to assume that, inasmuch as the symptoms are allergic in character and because the patient is allergically sensitized to the autogenous organism, it would be unwise to omit that organism from a treatment vaccine even though its responsibility for the symptoms has not been proved. In such a case Cooke's postulates[8] are only partly fulfilled by the presence of the skin reaction and the patient's acknowledged contact with the allergen.†

*See Table II.
†The allergen being an autogenous vaccine.

When, however, in addition to a positive vaccine skin reaction there regularly occurs either reproduction of the original symptoms or their relief,* it may be stated that the postulates are satisfied.

It is thus evident that the inference to be drawn from positive autogenous vaccine skin reactions are similar to those deducible from like reactions to other substances. They establish the existence of an allergic state, and they show that the testing material may be a potential cause of symptoms. The further evidence necessary to show that it is an actual cause of the symptoms appears to be at hand when repeated symptomatic or relief reactions follow vaccine injections in company with positive skin reactions.

3. Temporary relief of original allergic symptoms† has been rather frequently observed in company with positive skin reactions to vaccine injections. Unlike the case of the symptomatic reaction the occurrence of relief reactions has been noted also concomitantly with negative late skin reactions. We do not think that this last observation detracts from the validity of the late local vaccine reaction. It appears that a vaccine dose which is sufficient to produce temporary relief of original symptoms may yet be too small in amount to cause a positive late skin reaction.

4. Both the symptomatic reaction and the temporary relief reaction to vaccines have been repeatedly observed to occur alternately in the same patient after injection of the same vaccine and have appeared to depend upon the amount of vaccine injected; a relatively small dose being followed by a relief reaction, a symptomatic reaction following a larger dose.

5. Regression in intensity of the late local reaction has been regularly seen to accompany diminution in the degree of the original allergic symptoms during courses of therapeutic injections of vaccines.

6. After the injection of a vaccine there has at times been observed the lighting up of a former, but faded, late skin reaction to the same vaccine previously injected elsewhere on the patient's body.† A similar phenomenon has been noted by other workers in connection with therapeutic pollen and bacterial injections.[22, 30] Its significance is obscure but it suggests the presence of a specific reaction.

7. An extensive series of cross tests with vaccines, both autogenous and heterogenous, in human subjects, has been conducted by us. These tests have produced reactions which appear to indicate beyond doubt that early and late skin reactions vary with the recipients and are not constant with the vaccines themselves except in the case of repetition in the same patient.

8. Eosinophilia is accepted as an indication of the presence of allergy. Eosinophilia has been shown to be frequently present in positive late vaccine skin reactions sites.[34] Among these patients there has been repeatedly

*See Table II.
†Recurrent late local reaction; see Table II.

observed an association of eosinophilic reaction sites with symptomatic reactions.*

9. Seventy-one per cent of a series of 300 cases of asthma associated with infection and treated with autogenous vaccines, under the guidance of clinical reactions, obtained relief for periods of from three months to ten years.[33] Such a pragmatic test of successful application of vaccine skin reactions as guides, though suggestive, does not prove that the respective bacteria were responsible for the asthma that was relieved by their use in treatment, any more than does a skin reaction to a food protein and relief or symptoms following its withdrawal prove that the respective food is the cause of existing asthma. Nevertheless, favorable results following vaccine treatment, when considered in connection with constantly recurring skin reactions, would appear to offer corroborative evidence in favor of the specific action of vaccines, though failing as proof when taken alone.

Our vaccine methods and especially our claim for specificity in the case of the late vaccine skin reaction have been criticized unfavorably by Walzer.[7] He cites the fact that passive transfer of this (late) reaction has not been accomplished. With regard to this statement it should be said that the possibility of transferring local reactions is not present in all types of hypersensitiveness. For example, the Prausnitz-Küstner phenomenon does not occur in connection with contact dermatitis; yet the specific character of this form of hypersensitiveness is not generally denied. If we maintained that the late skin reaction is a manifestation of atopy, we would not question the necessity for demonstrating the possibility of the passive transfer of such reaction. The late vaccine skin reaction, however, appears to be associated with a type of hypersensitiveness which is distinct from atopy.

Many workers in immunology, both with animals and with human subjects† have recognized and investigated the late skin reaction to bacteria and their derivatives. The consensus of opinion seems to be that the occurrence of this reaction is reliable evidence of the presence of bacterial allergy.

Clinical allergists appear to have given but little attention to this reaction. Some of those who have commented upon it have expressed doubt as to its specific character. In fact the relationship between bacteria and infective asthma has been thought to be most obscure. Nevertheless Cooke, in a recent article,[9] has stated that "infective asthma may be regarded as an allergic reaction quite as properly as in that of the skin

*See Table II.

†Derick and Swift,[1] Ando,[2] Ando and Ozaki,[3] Andrewes, Derick and Swift,[4] Coburn,[5] Derick and Fulton,[11] Dick and Dick,[12] Dochet and Stevens,[13] Dorst and Morris,[14] Duval and Hibbard,[15] Ferry and Fisher,[18] Gay and Force,[19] Hansen-Preuss, Longcope and O'Brien,[21] Howell and Corrigan,[22] Irvine-Jones,[23] Julianelle and Avery,[24] Kaiser,[25] Mackenzie and Hanger,[26] Schwartzmann,[27] Swift and Derick,[28, 29] Swift, Hitchcock and Derick,[30] Swift, Wilson and Todd,[31] Von Pirquet,[36] Zinsser,[37] and Zinsser and Mallory.[38]

sensitive (atopic) type.'' He has also noted the fact that the hereditary background of infective asthma is the same as it is in the atopic form. He further founds his belief in the allergic character of infective asthma upon the rather frequently associated incidence of eosinophilia of the blood, tissues and secretions. Touart, Thomas and Russell[34] have recently found eosinophilia to be present at the sites of positive late vaccine skin reactions in patients with infective asthma, and they look upon this fact as corroborative evidence of the allergic character of these reactions and of a relationship between them and the original asthmatic symptoms.

The present trend of opinion in the profession appears to be swinging toward the acceptance of bacterial allergy as the etiologic factor in some types of asthma in the same manner as Swift,[30] Zinsser,[38] and others have associated it with rheumatic fever and some forms of arthritis.

SUMMARY

Study of human reactions to established allergic substances and to the intradermal injection of vaccines has furnished data upon which the present paper is based.

A classification of the types of human hypersensitiveness is offered.

Positive early and late vaccine skin reactions as observed are held to be specific phenomena and due to forms of hypersensitiveness.

Local, distant and general reactions to vaccine injections, as observed in hypersensitive individuals, are listed and briefly characterized.

A standard definition and description of the late vaccine skin reaction is tentatively offered.

A detailed description of the various features observed as characterizing the late positive vaccine skin reaction is presented.

A system of reading, recording and appraising the late vaccine skin reaction is proposed.

There is offered evidence that the late vaccine skin reaction is a specific phenomenon due to bacterial allergy.

CONCLUSION

The evidence herein presented seems to indicate that the late vaccine skin reaction is a specific phenomenon, due to bacterial allergy. As such it is a valuable guide (1) in the selection of autogenous vaccines for therapeutic use in conditions due to bacterial allergy, (2) in determining proper vaccine dosage, and (3) in fixing upon the best time for individual vaccine doses.

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THE IMPORTANCE OF THE CHENOPODIACEAE IN POLLINOSIS: WITH SPECIAL REFERENCE TO WINSLOW AND HOLBROOK, ARIZONA*

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IN THE several botanic surveys which have been made in California, Arizona, and New Mexico[1-11, 14] the wide variety of Chenopodiaceae has been indicated, although, with the exception of the survey by Dunn, not especially emphasized. In one area two or three species may be widely distributed, in another, an entirely new group may dominate the flora, and in the third area it is possible that the change may be even more pronounced than that between the first two. Possibly one prominent species will be found in several sections, and yet be completely absent from another.

Several interesting problems are presented to the student of allergy in this section of the United States. One of these concerns the etiologic specificity of the individual pollen; another, and one absolutely necessary to the solution of the former, is the exact distribution of the plants in question. If we assume an absence of biologic relationship between the pollen from the many species of Chenopodiaceae, then our treatment would of necessity be entirely dependent upon an accurate knowledge of the distribution of each species. On the other hand, if there be group relationships, we are equally eager to know the distribution of the groups, and of each member, although but one species is present in the area. We are attempting to aid in the solution of these problems by a careful study of skin hypersensitivity; by noting the relationship of these to the areas in which patients state their symptoms are produced; by treating with the "specific" pollen and by these botanic surveys. The surveys previously published by other investigators[1-5] have been entirely too general to be of much value in any particular area. In fact we have been very much handicapped by the inadequacy of taxonomic studies, and especially the lack of pictorial representation of many of these species. In a treatise by Coca[15] an attempt is made to correct this situation. His excellent photographs, with but a few exceptions, include none of the important species in the areas we have studied. As an example there might be cited his treatment of the genus Atriplex which he dismisses with a short description of each of two species and a pictorial representation of one of these (p. 684). In Figs. 13, 14, 15, and 16 we have tried to convey somewhat more clearly some of the characteristics of this particular species. The remainder of

*From the Allergy Clinic, Santa Fe Coast Lines, Hospital Association.

this survey and those previously published give nearly equal emphasis to several additional species of Atriplex.

It is our opinion that many of the photographs of plants or their habitats, published by the authors to which we have previously referred, add little to our knowledge and are practically useless as an aid in taxonomic studies. We have tried to prevent similar deficiencies by taking photographs in the field showing a close view of a habitat and, if important enough, the distribution of this plant over a large area. Most important of all we feel is the photographic representation, on a relatively large scale, of a characteristic pistillate, staminate, or perfect flowering branch. After photographing, the identification of this same branch is then checked in the laboratory. At the time that this series of photographs was taken, certain species were devoid of characteristic blossoms, fruit, or leaves, and hence it was necessary to use pressed specimens collected at other seasons of the year. Several attempts at photographing these yielded unsatisfactory results, and after numerous trials a method, which we wish briefly to describe, was evolved. With the kind assistance of Mr. L. Ergman, who operates the photostat machine at the Santa Fe general offices in this city, a direct photostatic reproduction has been made on 18″ by 24″ photostatic paper. By careful focusing with a hand lens on the ground glass plate it has been possible to represent clearly many minute details. The specimens are mounted on the dull black separator sheets found in the usual x-ray film package. In the direct print, of course, this appears white or very dull gray, and correspondingly all of the intensities in the cut are in the negative. The copper half-tone is made directly from this, and it is reduced as desired (Figs. 16 and 24-26). This method has several additional advantages over ordinary photographic processes in that it is relatively inexpensive, specimens of large diameters may be photostated, or small ones may be much magnified. These prints, when used in connection with a lecture, furnish a relatively simple and effective means of demonstration of the various types of plants. It is hoped that this method may be found of value by our readers.

As a result of our studies in the three states mentioned we were early impressed with the enormous variety of Chenopodiaceae in the Winslow-Holbrook area. This botanic group, therefore, will receive most emphasis. but other hay fever plants will be given such consideration as they merit.

We quite appreciate that many of our readers will not be trained botanists and moreover will be more or less unfamiliar with the flora of the western states. The details of the taxonomy of these several families and genera may be found in Standley's papers.[13] It may be of interest to mention briefly some of the important subdivisions under Chenopodiaceae, and a few of their characteristics.

The entire group may be called "salt loving" because they are especially

adapted to growth in soil so alkaline as to exclude most other plants. Thus we find certain of them distributed over the semi-arid sections of the west. Some other members of this group, such as spinach, garden and sugar beets, and Swiss chard, form an important source of food. The ornamental shrub firebush or summer cypress (*Kochia scoparia*) is well known. An important genus Chenopodium is widely distributed from east to west, and locally some are known as lamb's-quarters, Mexican tea, wormseed, and goosefoot. Even these wild forms are occasionally used for human as well as animal food.

The vegetation of the desert is frequently referred to as sagebrush. This classification is usually based upon the typical grayish appearance. Close examination will many times reveal the fact that these are not "sagebrush" but members of the genus Atriplex or saltbushes. Examples of this are shown in Figs. 7, 13 and 17. The common names for some of these species are silver-scale, wing-scale or shad-scale, allscale or cattle spinach, spiny saltbush, and red orache. Another sagelike species is *Eurotia lanata* or winter fat.

It must not be assumed that all desert vegetation is grayish or sagelike in appearance, as there are many notable exceptions, such as the light green greasewood (*Sarcobatus vermiculatus*) and the green succulent *Allenrolfea occidentalis*. The latter is similar in appearance to *Salicornia* or pickleweed, and incidentally is a profuse pollinator. One of the most common and perhaps the most troublesome weeds is the Russian thistle (*Salsola kali*). This is usually referred to as the tumble weed, but the true tumble weed, *Amaranthus graecizans*, is a member of the closely related pigweed family. This example and many we have cited above demonstrate the inadequacy of common names, many of which are purely local in usage. Not a few publications on this phase of allergy adhere to common instead of scientific names. This may make the paper more informative for the lay reader but renders it practically useless from a scientific standpoint.

We have already indicated that some of these species are of value as forage plants. When young and tender, Russian thistle may have the appearance of grass[11] and is relished by range stock. Winter fat, previously mentioned, undoubtedly received this name because of its importance as winter forage for sheep.

Winslow and Holbrook are included in one survey because their flora is somewhat similar, and in order to demonstrate that the findings are typical for a large area. From the sampling station on the west of Winslow to that on the east of Holbrook is a distance of about 65 miles. This section, with an altitude varying from 4,800 to 5,100 feet, is located in the basin of the Little Colorado River and has a soil of the alluvial type. The present river bed passes through the town of Holbrook and comes about two and

one-half miles to the north and also to the east of Winslow. The Inez Mesa is north of Holbrook and extends westward toward Winslow. To the south and slightly west of Holbrook one finds the Pink Cliffs and in the same relative position with respect to Winslow, but somewhat further distant is an unnamed ridge which is heavily wooded with pine and which forms the drainage area for Clear Creek. This ridge is reached from Winslow by the Sunset Pass Road.

The type, abundance and duration of growth of vegetation are primarily governed by the combination of edaphic, climatic and topographic factors. Temperature and precipitation are among the most important of these factors, and two recent annual records of each (Figs. 1, 2, 3, and 4) are included in this paper. Like Seligman, Arizona, this section experiences several months of winter weather, making its most active growing

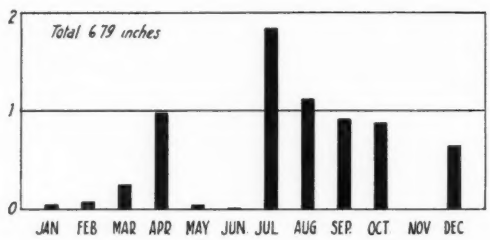

Fig. 1.—Monthly and total rainfall for Winslow, Arizona, during 1924.

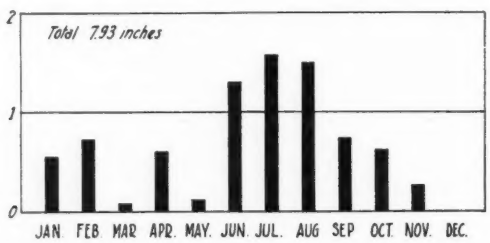

Fig. 2.—Monthly and total rainfall for Winslow, Arizona, during 1925.

period about 160 days in length, beginning the latter part of April and extending until the first frost which occurs in the latter part of September or the early part of October. Likewise, the summer is characterized by the highest temperatures and the most abundant rainfall, which bespeak a long and prolific season of pollination.

By making a primary survey of these two towns the best periods for the intensive study, to be made the following year, were decided upon as May, the peak of the spring season, and August, the height of the summer-fall season. Each of these communities was divided into sections, and a representative sampling station in each was studied in detail. The

same methods for making a survey as were previously described[9, 11] are employed in this study.

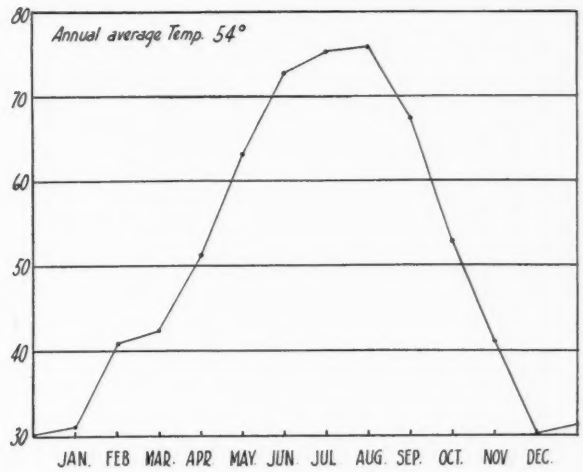

Fig. 3.—Monthly and annual average temperatures for Winslow, Arizona, during 1924.

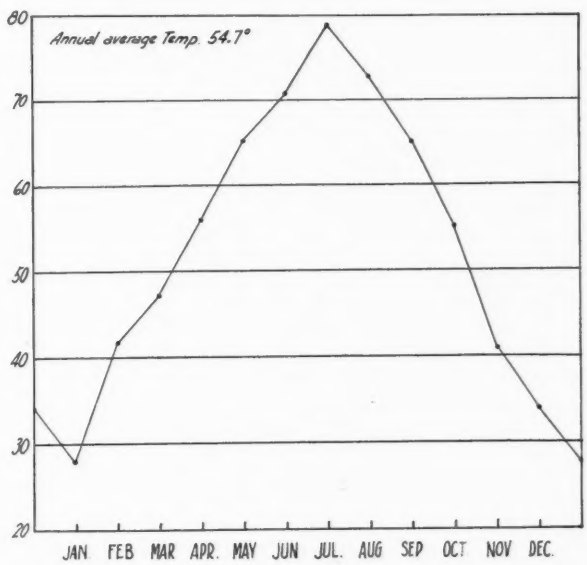

Fig. 4.—Monthly and annual average temperatures for Winslow, Arizona, during 1925.

WINSLOW, ARIZONA

This town, with a population of approximately 5,000, is an important division point on the Santa Fe Railroad. It is the residence of a large number of railroad employees, many of whom work between it and Seligman on the west or to Gallup, New Mexico, on the east. The topography

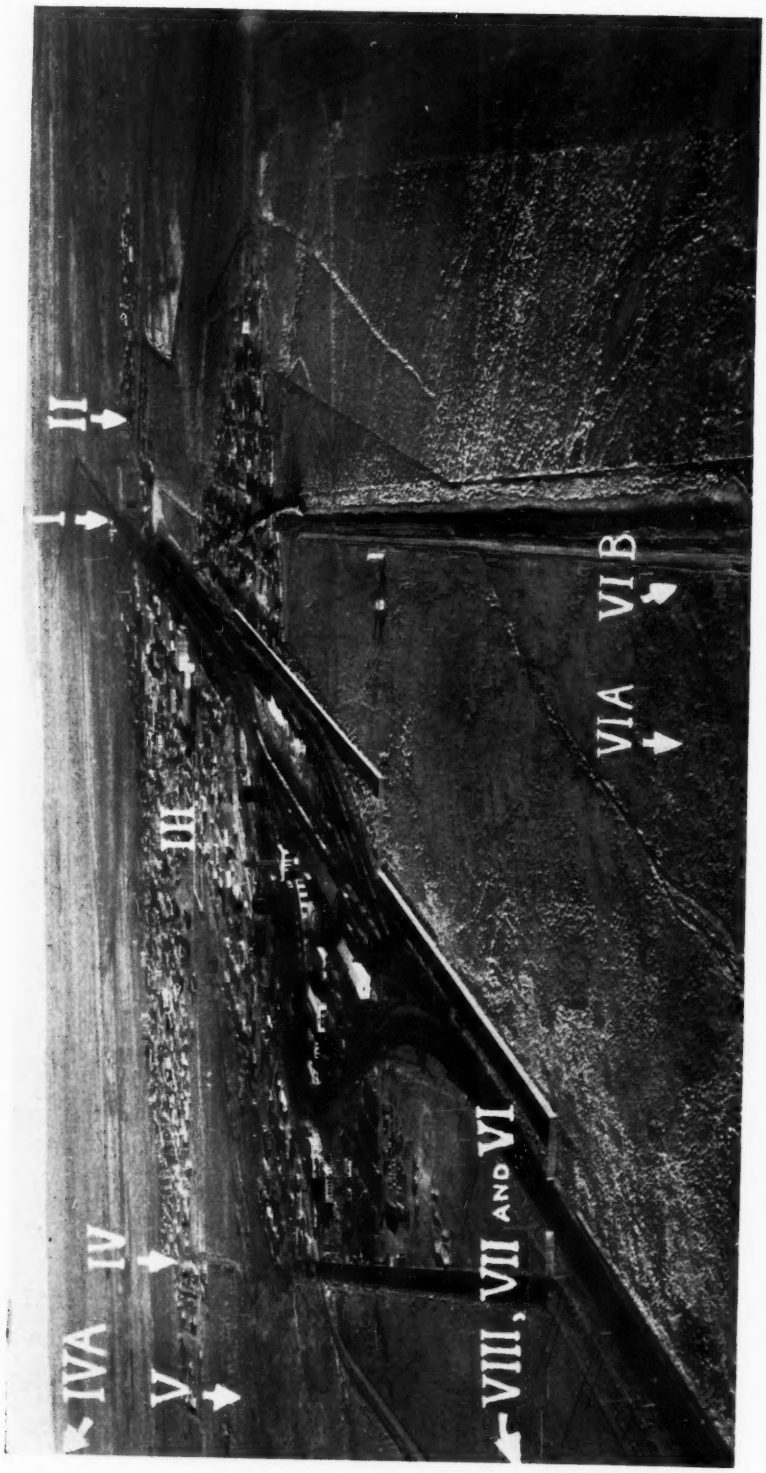

Fig. 5.—Aerial photograph of Winslow, Arizona.

and the location of some of the most important sampling stations may best be indicated by reference to the aerial photograph* (Fig. 5). A short discussion of each area may not be amiss.

Station I, located on the edge of the town, is north of the railroad tracks and includes an area on each side of the highway. Here (Fig. 6) the vegetation is characterized by an abundance and variety of Chenopodiaceae. *Atriplex expansa* (Fig. 25), *A. confertifolia* (Figs. 7, 8 and 9), *Dondia sp.* and *Sporobolus airoides* (Fig. 10) occur as very abundant codominants,

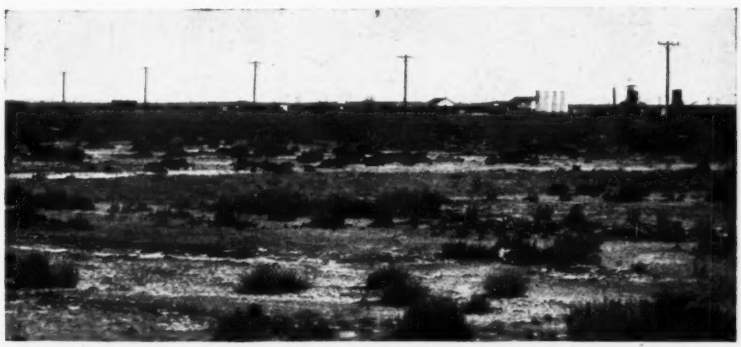

Fig. 6.—General view of Station I, Winslow, looking south toward the railroad tracks. *Atriplex confertifolia* and *Atriplex expansa* dominate the foreground, and *Salsola kali* appears beyond the road.

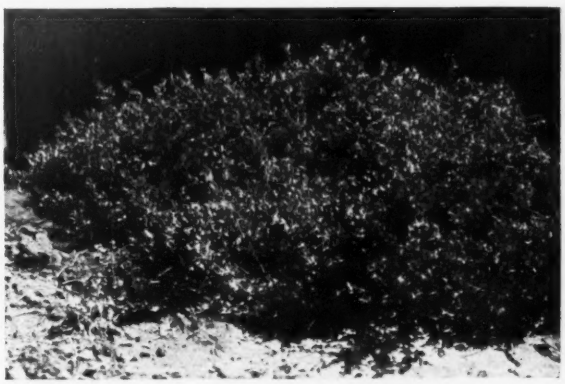

Fig. 7.—Habit view of *Atriplex confertifolia.*

and with them, but somewhat less abundant, are *Allenrolfea occidentalis* (Figs. 11 and 12), *Atriplex canescens* (Figs. 13, 14, 15 and 16), *A. jonesii* (Figs. 17, 18 and 19), *A. rosea, Salsola kali* and *Distichlis spicata* (Figs. 20 and 21). With these there are a number of Compositae.

Station II is located in a slight depression on the Clear Creek Road, south of town and 300 yards from the railroad track. Here the codom-

*This and the photograph of Holbrook were made in January, 1932, by the 23rd Photo Section, Air Corps, U. S. Army. We are deeply indebted to the Commanding Officer, March Field, California, for permission to use these photographs.

Fig. 8.—A single branch of *Atriplex confertifolia*, showing leaves and a few "spiny" branchlets.

Fig. 9.

Fig. 10.

Fig. 9.—*Atriplex confertifolia*, the mature fruiting bracts.
Fig. 10.—Habit of *Sporobolus airoides* in the typical bunch.

inants are *Atriplex confertifolia* and *Sporobolus airoides*, with *Gutierrezia sarothrae* occurring less abundantly. As one continues south on Clear Creek Road the vegetation becomes more scattered. At a spot one mile southeast of Clear Creek Bridge, *Hilaria jamesii* replaces *Sporobolus*

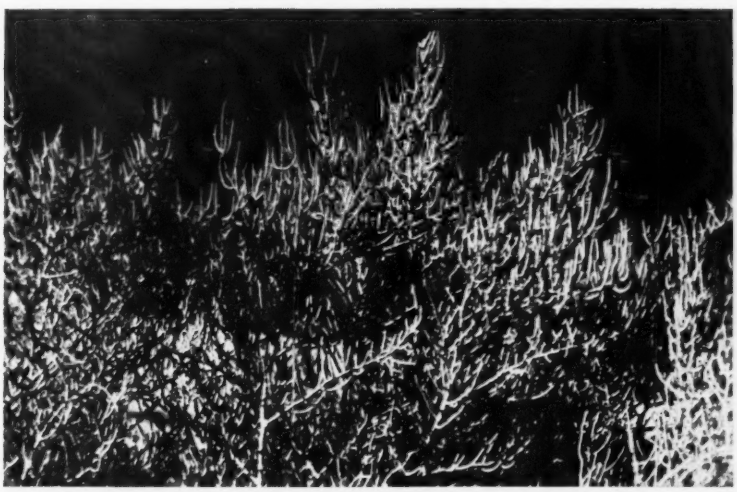

Fig. 11.—*Allenrolfea occidentalis*, a section of a habit. Plant is in flower.

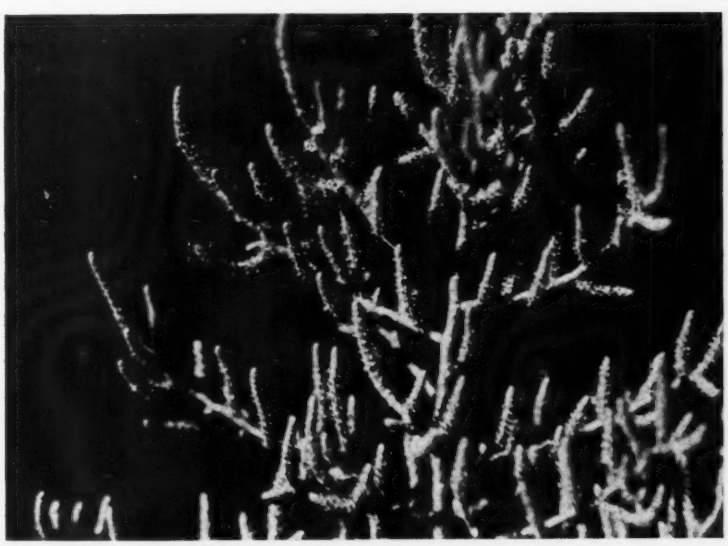

Fig. 12.—*Allenrolfea occidentalis*, a section of a branch showing the flowers in full pollination.

airoides as the codominant of *Atriplex confertifolia*. A few other grasses as well as *Salsola kali* and several composites are present at well spaced intervals. The importance of this and the previous station is magnified by the fact that they are in the direct path of the prevailing east winds.

Station III, the entire inhabited area, cannot readily be designated on the photograph. It has a vegetation composed of cultivated plants as well

Fig. 13.—*Atriplex canescens*, a large staminate plant with a dwelling in background indicating the relative size.

Fig. 14.—*Atriplex canescens*, pistillate plant bearing mature fruit. *Salsola kali* makes up the immediate foreground.

as the native flora. The lawns are mostly sown to *Poa pratensis* and *Lolium perenne*, but quite a bit of *Cynodon dactylon* is also present. Of the trees, *Populus fremontii* is by far the most abundant. Of secondary im-

portance are the cypress, locust and tamarisk. The only cultivated shrub of much significance is the *Kochia scoparia* or firebush, which commonly

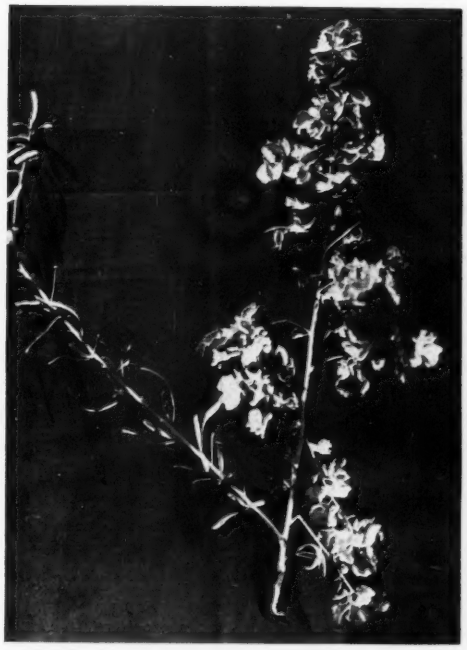

Fig. 15.

Fig. 16.

Fig. 15.—*Atriplex canescens*, mature branch showing "wing-scale" fruit.
Fig. 16.—*Atriplex canescens*, a staminate branch in full pollination.

Fig. 17.

Fig. 18.

Fig. 17.—*Atriplex jonesii*, a habit with the staminate flowers showing on the ends of the branches.
Fig. 18.—A mature pistillate branch of *Atriplex jonesii* with clusters of fruiting bracts in the axils of the leaves.

escapes from cultivation. Along the roads, especially in the western part of town near the Round House, there are many ruderals. Among the most important are *Atriplex confertifolia, A. rosea, A. expansa, Salsola*

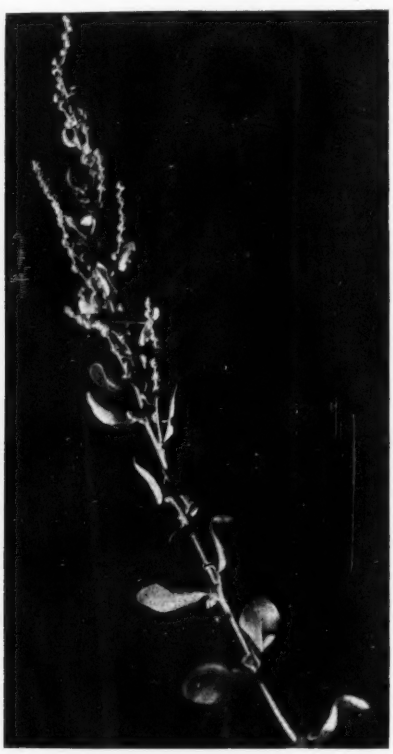

Fig. 19.—A single branch of *Atriplex jonesii* bearing the mature staminate flowers.

Fig. 20.—A general habit view of *Distichlis spicata.*

kali and *Amaranthus retroflexus.* A few grasses such as *Distichlis spicata, Cynodon dactylon* and *Echinochloa crusgalli* are found. Here, in contrast to the other stations, *Xanthium canadense* is rather abundant.

Station IV, one mile directly north of town, is quite typical of the *Atriplex confertifolia-Gutierrezia sarothrae* association (Fig. 22) frequently described[12] for this section of the country. More commonly associated

Fig. 21.—*Distichlis spicata,* several staminate heads in full pollination.

Fig. 22.—*Atriplex confertifolia—Gutierrezia sarothrae* association near Station IV, Winslow. Many *Populus fremontii* can be seen in the background.

with these are *Sporobolus airoides, Salsola kali* and *Dondia* sp. About five miles north of town (IV A) is a large salt flat (Tucker's) dotted with a very scant vegetation. There are no large shrubs or herbs. *Sporobolus airoides* (alkali saccaton) occurs in scattered clumps, and in certain

limited areas *Atriplex confertifolia* is rather common. A few *Atriplex canescens* are present in the less saline locations.

Station V is located on Cemetery Road two miles northwest of the center of the town. The vegetation, although less scattered, is very similar in many respects to that on Tucker's Flat in that *Sporobolus airoides* is the dominant grass and *Atriplex confertifolia* is present in certain areas. In addition *Gutierrezia sarothrae* is rather common and occasionally *Atriplex canescens* and *Aristida* sp. are associated with it.

Station VI, directly west of town at the junction of Sunset Pass Road and the highway, contains *Sporobolus airoides* and *Atriplex canescens.* These are very abundant and *Hilaria jamesii* is rather common. As one goes south on Sunset Pass Road, *Artemisia bigelovii* appears at about 0.2 mile out, and at 2.6 miles further south the physiognomy is practically the same.

Station VII is on the main highway, 2.5 miles west of town. Here again *Atriplex jonesii* and *A. confertifolia* occur as common codominants and *Aristida wrightii* is likewise very common.

Station VIII is about 30 miles west of Winslow and is included in this paper, although it is rather distant from town, because it indicates the proximity of the woodland type of vegetation. This station is at a higher elevation, and correspondingly the vegetation is of an entirely different type. *Pinus ponderosa var. bractyptera* is very abundant and a few *Juniperus monosperma* are also present. *Artemisia bigelovii* and *Koeleria cristata* are the only other hay fever causing plants found in sufficient abundance to be significant.

The findings at each of the eight sampling stations are condensed in Table I. Here the botanic families as well as genera and species are given. The common names of each of these, when sufficiently well established, are also indicated. The occurrence of any species is designated by one or more asterisks (see key at the foot of the table). The absence of an asterisk does not absolutely exclude a particular plant; although it was not found on the several survey trips over a period of two years. The approximate season of pollination has been shown in the column at the right. This will of course vary with the location, exposure, and the general climatic conditions for any particular year.

A superficial analysis of Table I will indicate the nearly complete absence of grasses, except *Sporobolus airoides* and *Hilaria jamesii,* the similar absence or unimportance of the composites and the dominance of members of the Chenopodiaceae, several species of which have never been mentioned in previous discussions of pollinosis. If this survey be compared with others made in the Arizona-New Mexico territory, it will be seen that Russian thistle (*Salsola kali*) is here relatively unimportant. In several instances it will be noted that a particular plant will be entirely lacking from seven out of the eight stations, yet be quite important at the remain-

TABLE I

BOTANIC SUMMARY OF WINSLOW, ARIZONA

SCIENTIFIC NAME	COMMON NAME	STATIONS I	II	III	IV	IVA	V	VI	VII	VIII	SEASON OF POLLINATION
CUPRESSACEAE	CYPRESS FAMILY										
Juniperus monosperma	One-seeded juniper	–	–	**	–	–	–	–	–	**	Sp.
PINACEAE	PINE FAMILY										
Pinus ponderosa bractyptera	Yellow pine	–	–	–	–	–	–	–	–	****	Sp.
EPHEDRACEAE	JOINT-FIR FAMILY										
Ephredra sp.		–	–	–	–	–	–	**	–	–	
GRAMINEAE	GRASS FAMILY										
Agropyron richardsoni	Wheat grass	–	–	–	–	–	–	–	–	**	Sp.
Aristida purpurea var. longiseta	Wiregrass	–	–	–	–	–	**	–	–	–	Sp.
Aristida wrightii	Wright's aristida	–	*	–	–	–	–	–	**	–	Sp.
Bouteloua hirsuta	Black grama	–	**	–	–	–	–	***	–	–	
Bromus unioloides	Rescue grass	–	–	–	–	–	–	–	**	–	Sp.
Cynodon dactylon	Bermuda grass	–	–	**	–	–	–	–	–	–	Sp. Sm.
Distichlis spicata	Salt grass	***	–	**	–	–	–	–	–	–	Sp.
Echinochloa crusgalli var. zelayensis	Mexican barnyard grass	–	–	**	–	–	–	–	–	–	Fl.
Hilaria jamesii	James' galleta	–	***	–	–	–	***	***	–	–	Sp.
Hordeum jubatum	Squirrel tail	–	–	**	–	–	–	–	–	–	Sp.
Hordeum murinum	Wall barley	–	–	**	–	–	–	–	–	–	Sp.
Koeleria cristata	Koeler's grass	–	–	–	–	–	–	–	–	***	Sp.
Lolium perenne	Perennial rye grass	–	–	**	–	–	–	–	–	–	Sp. Sm.
Melica porteri	Melic grass	–	–	**	–	–	–	–	–	–	Sp.
Poa pratensis	Kentucky blue grass	–	–	**	–	–	–	–	–	–	Sp. Sm.
Sporobolus airoides	Alkali saccaton	****	****	–	***	**	**	****	–	–	Sp. Sm.
Triodia pulchella	Low triodia	–	**	–	–	–	–	****	–	–	Sp. Sm.

* = present or rare.
** = fairly common, few.
*** = common.
**** = very common or abundant.

– = does not occur.
Fl. = pollinates in the fall.
Sp. = pollinates in the spring.
Sm. = pollinates in the summer.

TABLE I (CONTINUED)

SCIENTIFIC NAME	COMMON NAME	STATIONS I	II	III	IV	IVA	V	VI	VII	VIII	SEASON OF POLLINATION
CYPERACEAE	SEDGE FAMILY										
Scirpus sp.	Bulrush	–	–	–	**	–	–	–	–	–	
SALICACEAE	WILLOW FAMILY										
Populus fremontii	Fremont cottonwood	–	–	***	–	–	–	***	–	–	Sp.
CHENOPODIACEAE	SALTBUSH FAMILY										
Allenrolfea occidentalis	Burro weed	***	–	–	–	–	–	–	–	–	Fl.
Atriplex canescens	Shad-scale	***	**	–	–	**	**	****	–	–	Sp. Sm.
Atriplex confertifolia	Spiny saltbush	****	****	***	–	***	***	–	****	–	Sm.
Atriplex expansa		****	–	–	–	–	–	–	–	–	Fl.
Atriplex jonesii		***	–	–	****	–	–	–	***	–	Sm. Fl.
Atriplex rosea	Red orache	***	–	**	–	–	–	–	–	–	Fl.
Chenopodium album	Lamb's-quarters	**	–	–	–	–	–	–	–	–	Fl.
Dondia sp.		****	*	–	***	–	–	–	–	–	Fl.
Eurotia lanata	Winter fat	–	–	–	–	–	–	**	–	–	Sm.
Kochia scoparia	Firebush	–	–	***	–	–	–	****	–	–	Sm.
Salsola kali	Russian thistle	***	**	–	***	–	–	–	–	–	Fl.
AMARANTHACEAE	PIGWEED FAMILY										
Amaranthus sp.		–	–	**	–	–	–	–	–	–	Sm.
Amaranthus retroflexus	Rough pigweed	–	–	**	–	–	–	–	–	–	Fl.
LEGUMINOSAE	PEA FAMILY										
Robinia pseudacacia	Black locust	–	–	***	–	–	–	–	–	–	Sm.
MALVACEAE	MALLOW FAMILY										
Sphaeralcea arizonica		–	–	–	–	–	–	**	–	–	Sp. Sm.
CACTACEAE	CACTUS FAMILY										
Opuntia sp.		**	–	***	–	–	–	–	–	–	Sm.

TABLE I (CONTINUED)

SCIENTIFIC NAME	COMMON NAME	STATIONS I	II	III	IV	IVA	V	VI	VII	VIII	SEASON OF POLLINATION
TAMARICACEAE	TAMARIX FAMILY										
Tamarix gallica	Salt cedar	**	–	**	–	–	–	–	–	–	Sp. Sm.
ASCLEPIADACEAE	MILKWEED FAMILY										
Asclepias mexicana	Narrow-leaf milkweed	**	**	–	–	–	–	–	–	–	Sp. Sm.
BORAGINACEAE	BORAGE FAMILY										
Lithospermum sp.	Puecoon	–	–	–	–	–	–	**	–	–	Sp.
LABIATAE	MINT FAMILY										
Salvia carnosa	Sage	–	–	–	–	–	–	–	–	**	Sp.
SOLANACEAE	NIGHTSHADE FAMILY										
Solanum sp.	Nightshade	**	–	**	**	–	–	–	–	–	Sp.
SCROPHULARIACEAE	FIGWORT FAMILY										
Castilleia sp.		–	–	–	–	–	–	**	–	–	Sp. Sm.
COMPOSITAE	SUNFLOWER FAMILY										
Artemisia bigelovii		–	**	–	–	–	–	***	–	–	Late Fl.
Artemisia sp.		–	*	–	–	–	–	–	–	***	Late Fl.
Erigeron multabile	Fleabane	–	–	–	–	–	–	***	–	–	Sp.
Gaillardia sp.		–	–	–	–	–	–	***	–	–	Sm.
Gutierrezia sarothrae	Matchweed	**	***	–	***	–	**	***	–	–	Fl.
Helianthus annuus	Common sunflower	–	–	–	**	–	–	–	–	–	Fl.
Isocoma wrightii	Rayless goldenrod	**	–	–	–	–	–	–	–	–	Sp.
Senecio aeris	Groundsel	–	–	–	–	–	–	**	–	–	Sp.
Senecio filifolius	Groundsel	**	–	–	–	–	–	–	–	**	Sp.
Xanthium canadense	Cockle bur	**	–	–	***	–	–	–	–	–	Sm.

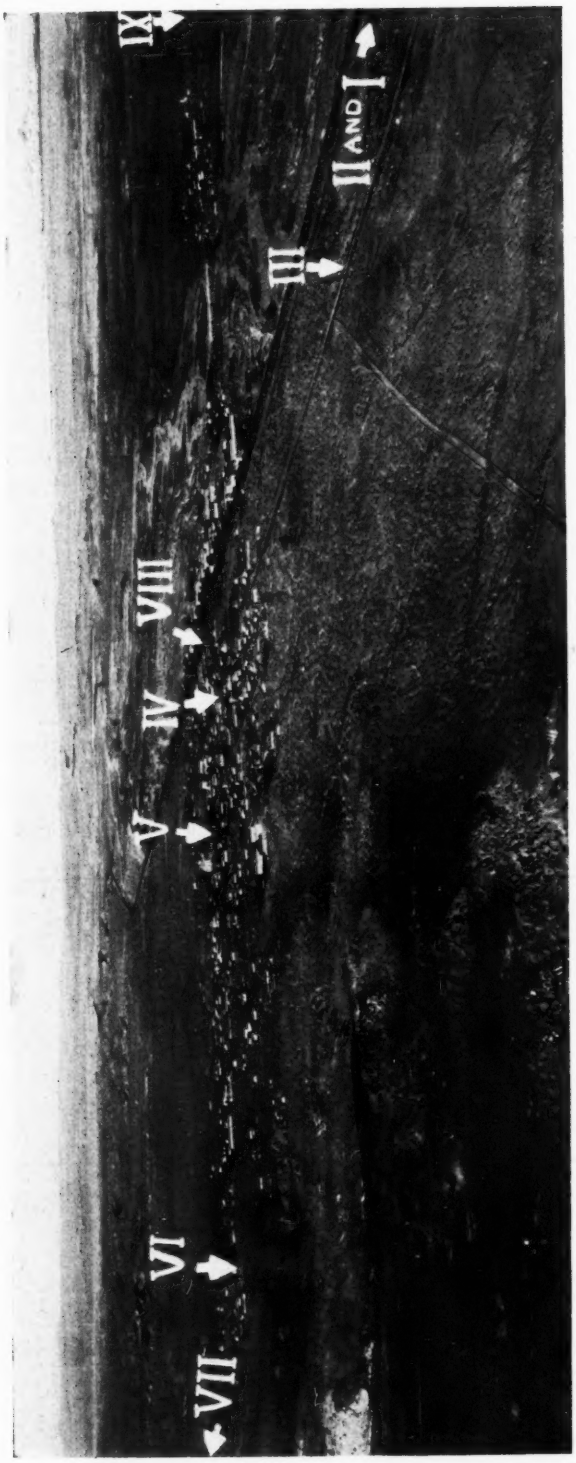

Fig. 23.—An aerial photograph of Holbrook, Arizona.

ing one. In fact there is no one plant which occurs at more than five of the eight stations. This again emphasizes the inadequacy of cursory surveys.

HOLBROOK, ARIZONA

The county seat of Navajo County has a population of about 1500. As previously mentioned the altitude is only slightly greater than that of Winslow. The excellent aerial photograph (Fig. 23) enables one to designate quite accurately many of our sampling stations in this area. In this

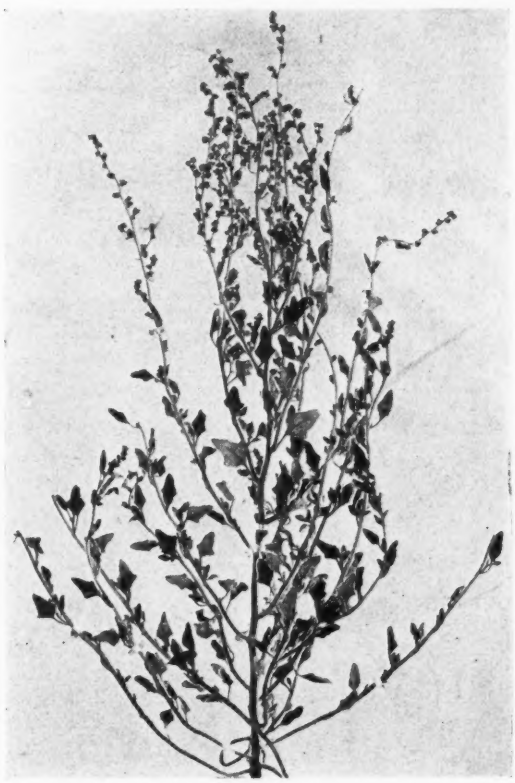

Fig. 24.—*Chenopodium incanum.*

as in the photograph of the Winslow section the many dots in the foreground represent, in the main, Chenopodiaceae. A brief description of each sampling station is given in the following paragraphs.

Station I, located at a point 16 miles west, emphasizes the extreme importance of the Chenopodiaceae throughout this territory. *Sarcobatus vermiculatus* and *Atriplex powellii* are very abundant; *A. jonesii, A. canescens* and *Salsola kali* of less importance; and a number of *Foresteria neomexicana* are scattered throughout. The importance of this and other stations on the west of town, as well as those on the south, is enhanced by the prevailing southwesterly winds.

Station II, along the same highway at a distance of five miles west of town, shows a slight variation from the usual predominance of the Chenopodiaceae by the codominance of *Atriplex confertifolia* with *Gutierrezia glomerella*. *Atriplex canescens* is common throughout, and *Artemisia bigelovii* and *Sporobolus airoides* are of minor importance.

Station III is along Highway 66, only one mile west, in an alkaline flat. Except for the abundance of *Distichlis spicata* the vegetation is mainly composed of Chenopodiaceae. Most abundant of these are *Atriplex canes-*

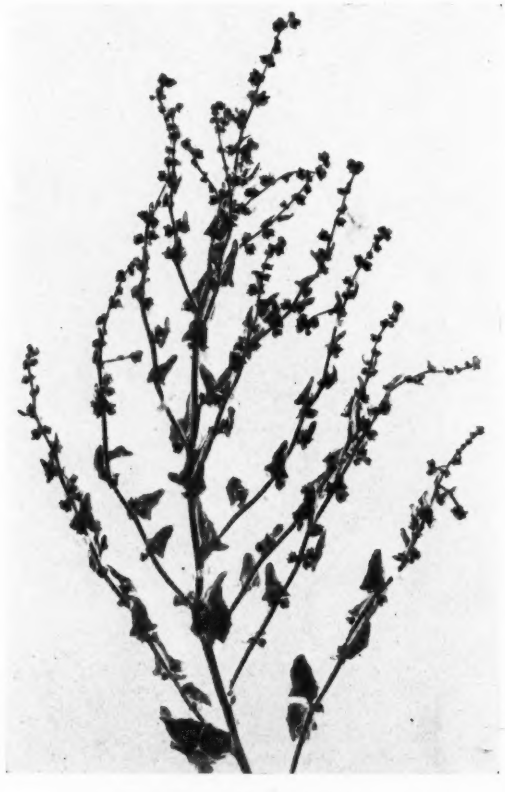

Fig. 25.—*Atriplex expansa.*

cens, Sarcobatus vermiculatus and *Salsola kali;* however *Atriplex rosea, Chenopodium incanum* (Fig. 24) and *Atriplex confertifolia* are rather numerous. *Franseria tenuifolia* is equally common but is limited to the immediate vicinity of the highway.

Station IV is in the town, on the north side and just west of the main street. Here again the major portion of the area is occupied by Chenopodiaceae. The most important are *Dondia suffrutescens, Atriplex rosea* and rather commonly *Salsola kali.* Likewise the only abundant grass is *Sporobolus airoides.* Two trees, *Forestiera neomexicana* and *Populus fremontii* are fairly common.

Station V, on the east edge of town, contains many of the same plants found in the other sampling stations of the inhabited area, with a few additions. Here again the dominance of the Chenopodiaceae is unquestioned.

Fig. 26.—*Chenopodium leptophyllum.*

Fig. 27.—Growth of *Salsola kali* in the inhabited area, Holbrook.

Atriplex expansa (Fig. 25) is very abundant, and of the grasses *Sporobolus airoides* is the most prominent. *Allenrolfea occidentalis, Atriplex canescens, A. jonesii, Dondia suffrutescens, Salsola kali* and *Distichlis spicata* are common in this area. A number of other plants of importance also are found.

TABLE II

BOTANIC SUMMARY OF HOLBROOK, ARIZONA

SCIENTIFIC NAME	COMMON NAME	STATIONS I	II	III	IV	V	VI	VII	VIII	IX	SEASON OF POLLINATION
GRAMINEAE	GRASS FAMILY										
Bouteloua curtipendu'a	Side-oats grass	–	–	–	–	–	–	–	–	***	Sm.
Bouteloua gracilis	Blue grama	–	–	**	–	–	–	–	–	***	Sp.
Bouteloua radicosa	Purple grama	–	–	–	–	–	–	–	–	**	Sm.
Bromus tectorum	Downy brome-grass	–	–	–	–	–	–	–	**	–	Sp.
Bromus sp.		–	–	–	**	–	–	–	–	–	Sp.
Distichlis spicata	Salt grass	–	–	****	–	***	–	–	***	–	Sp.
Hilaria jamesii	James' Galleta	–	**	–	–	–	–	****	–	***	
Hordeum jubatum	Squirrel tail	–	–	**	–	–	–	–	**	–	Sp.
Hordeum murinum	Wall barley	–	–	–	–	–	–	–	**	–	Sp.
Melica porteri	Melic grass	–	–	–	**	–	–	–	–	–	Sp.
Muhlenbergia porteri	Mesquite grass	–	–	–	–	–	–	***	–	–	
Oryzopsis sp.	Mountain rice	–	–	–	–	–	–	–	–	**	Sm.
Sporobolus airoides	Hair-grass dropseed	**	***	–	****	****	***	**	****	–	Sp. Sm.
Triodia pulchella	Low triodia	–	–	–	–	–	–	–	–	**	Sm.
SALICACEAE	WILLOW FAMILY										
Populus fremontii	Fremont cottonwood	–	***	–	**	***	–	–	–	–	Sp.
Populus alba	White cottonwood	–	–	–	–	**	–	–	–	–	Sp.
POLYGONACEAE	BUCKWHEAT FAMILY										
Polygonum sp.		–	–	–	–	–	–	–	***	–	Sm.
Rumex crispus	Curly dock	–	*	–	–	–	–	–	–	–	Sm.

* = present or rare.
** = fairly common, few.
*** = common.
**** = very common or abundant.

– = does not occur.
Fl. = pollinates in the fall.
Sp. = pollinates in the spring.
Sm. = pollinates in the summer.

TABLE II (CONTINUED)

SCIENTIFIC NAME	COMMON NAME	STATIONS I	II	III	IV	V	VI	VII	VIII	IX	SEASON OF POLLINATION
CHENOPODIACEAE	SALTBUSH FAMILY										
Allenrolfea occidentalis	Burro weed	–	–	–	–	***	–	–	–	–	Fl.
Atriplex canescens	Shad-scale	**	***	****	–	***	***	**	–	–	Sp. Sm.
Atriplex confertifolia	Spiny saltbush	–	****	***	–	–	–	–	–	–	Sm.
Atriplex expansa		–	–	–	–	****	–	–	–	–	Fl.
Atriplex jonesii		***	–	–	–	***	–	–	–	–	Sm. Fl.
Atriplex powellii		****	–	–	–	–	–	–	–	–	Sm. Fl.
Atriplex rosea	Red orache	–	–	***	***	**	***	–	****	–	Fl.
Atriplex wrightii		–	–	–	–	–	–	–	***	–	Fl.
Chenopodium album	Lamb's-quarters	–	–	–	–	–	–	–	**	–	Fl.
Chenopodium incanum		–	–	***	–	–	–	***	–	–	Fl.
Chenopodium leptophyllum		–	–	–	–	–	–	***	***	–	Fl.
Dondia suffrutescens		–	–	–	****	***	–	–	–	–	Sm.
Eurotia lanata	Winter fat	–	–	–	–	–	–	–	**	–	Sm.
Kochia scoparia	Firebush	–	–	–	–	**	–	–	**	–	Sm.
Sarcobatus vermiculatus	Black greasewood	****	–	****	–	–	***	–	–	–	Sm. Fl.
Salsola kali	Russian thistle	**	–	****	**	***	****	**	****	–	Sm.
AMARANTHACEAE	AMARANTH FAMILY										
Amaranthus blitoides		–	–	–	–	–	–	–	**	–	Fl.
CAPPARIDACEAE	CAPER FAMILY										
Cleome lutea		–	–	–	–	–	–	–	**	–	Fl.
Cleome serrulata	Bee-plant	–	–	–	–	–	–	–	–	**	Fl.
ROSACEAE	ROSE FAMILY										
Cowania stansburiana	Cliff rose	–	–	–	–	–	–	–	–	**	Sp.

TABLE II (CONTINUED)

SCIENTIFIC NAME	COMMON NAME	STATIONS I	II	III	IV	V	VI	VII	VIII	IX	SEASON OF POLLINATION
LEGUMINOSAE	PEA FAMILY										
Prosopis sp.	Mesquite	–	–	–	**	–	–	–	–	–	Sp.
EUPHORBIACEAE	SPURGE FAMILY										
Euphorbia eremica	Spurge	–	–	–	–	–	–	–	–	*	Sm.
ZYGOPHYLLACEAE	CALTROPS FAMILY										
Tribulus terrestris	Burnut	–	–	–	–	–	–	**	–	–	
MALVACEAE	MALLOW FAMILY										
Sphaeralcea arizonica		–	–	–	***	–	–	**	–	–	Sp. Sm.
OLEACEAE	ASH FAMILY										
Forestiera neomexicana	Ironwood	***	–	–	***	–	–	–	–	–	Sp.
POLEMONIACEAE	GILIA FAMILY										
Gilia longiflora		–	–	–	–	–	–	***	–	–	Sm.
SOLANACEAE	NIGHTSHADE FAMILY										
Solanum sp.		–	–	–	**	–	–	–	–	–	Sm.
COMPOSITAE	SUNFLOWER FAMILY										
Artemisia bigelovii		–	***	–	–	–	–	–	**	–	Late Fall
Franseria tenuifolia	False ragweed	**	–	****	–	–	*	**	–	****	Fl.
Gutierrezia glomerella	Snakeweed	–	****	–	–	–	***	***	**	**	Fl.
Helianthus annuus	Common sunflower	–	–	**	–	–	–	**	–	**	Sm. Fl.
Senecio sp.	Groundsel	–	–	–	–	–	–	–	**	–	Sp.

Station VI, along Highway 66 but one-fourth mile north of Holbrook, presents a similar picture with *Salsola kali* and *Sarcobatus vermiculatus* as the abundant Chenopodiaceae. *Atriplex canescens* is quite common and *A. powellii* less so. *Sporobolus airoides* is the only significant grass, and a few *Gutierrezia glomerella* and *Franseria tenuifolia* are associated.

Station VII is located on a higher plateau three miles east along the highway. Here the vegetation consists of a larger variety of plants. Of the grasses, *Hilaria jamesii* is abundant and *Muhlenbergia porteri* common. *Atriplex incanum* and *Chenopodium leptophyllum* (Fig. 26) are the most common among the Chenopodiaceae.

Station VIII is on the south side of town at the junction of the main street and the Santa Fe Railroad tracks. It is just north of the railroad station and comprises an area on either side of the street. The prominence of Chenopodiaceae is the striking feature of this station. *Atriplex rosea* and *Salsola kali* (Fig. 27) are abundant and *Atriplex wrightii* and *Chenopodium leptophyllum* are common. *Sporobolus airoides* is very common and *Distichlis spicata* somewhat less so.

Station IX, one mile south of town, is on the McNary Road just south of the Springerville branch. This station, of slightly higher elevation than the town and devoid of the influences of man, has a vegetation of the desert plains type. *Bouteloua curtipendula, B. gracilis* and *Hilaria jamesii* are the most common grasses but many others are also present. Along the roadside *Franseria tenuifolia* is very abundant.

These data for the nine sampling stations are presented in a composite form in Table II. This differs somewhat from that of the Winslow area. It is noticed that grasses are perhaps more widely distributed; composites, with the exception of *Franseria tennuifolia*, are here even less numerous, and that additional members of the Chenopodiaceae have made their appearance.

SUMMARY

The key to the approximate season of pollination in each of the two tables discloses the three seasons: spring, summer and fall. Each of these might be subdivided into early or late and would vary more or less with local conditions. The early spring season would probably be limited to the pollination of the cottonwoods, *Populus fremontii;* but in the Winslow region, possibly the pollen of *Pinus edulis* or *Pinus ponderosa var. bractyptera* would be an additional factor. These pollens would of necessity come long distances from either the Flagstaff or Sunset Pass area. This is in contrast to our findings at Flagstaff, Arizona, and Gallup, New Mexico, which are to be published.

Grasses are undoubtedly the most significant source of spring pollens, but here again one must indicate the particular species concerned. For example, the two tables disclose the relative insignificance of *Cynodon dactylon* in Winslow and its absence from the sampling stations at Holbrook. In contrast to this, one should keep in mind the surveys of Phillips

in the region of Phoenix, Arizona, where *Cynodon dactylon* is of maximum importance. These tables indicate the importance of *Sporobolus airoides,* especially in Holbrook. Of secondary significance are *Hilaria jamesii* and *Distichlis spicata.* The latter is somewhat more abundant in Holbrook. In passing, it might be of interest to note the absence of the common eastern grasses; furthermore, we call attention to several potential hay fever grasses not previously discussed from this standpoint.

The major season is undoubtedly a summer and early fall period, and incidentally this corresponds to the period most often emphasized in the patients' complaints. In this season the Chenopodiaceae or saltbush family occupies the most prominent position. The one species of this family, found at the greatest number of sampling stations in the entire area is *Atriplex canescens.* In Winslow, however, it is superseded in distribution and importance by *Atriplex confertifolia* which occupies but a minor position in Holbrook. *Atriplex powellii* and *A. wrightii,* each of major importance in one of the nine stations of this area, are completely absent from Winslow, and *Atriplex rosea* secondary in significance at Holbrook is limited in its distribution to two stations at Winslow. Two members of a genus closely related to *Atriplex, Chenopodium incanum* and *C. leptophyllum* of such importance in Holbrook are likewise absent from Winslow. Holbrook is further characterized by the significant presence of *Sarcobatus vermiculatus,* a plant not found in Winslow, and by the wide and intensive distribution of *Salsola kali* as compared to any single Chenopodiaceae in the area, while in Winslow it is of less prominence. These comparisons could be carried throughout the various botanic subdivisions and should give added weight to our contention that occurrence of a particular species in a limited locality is a worthless criterion of its significance in the entire community. On a larger scale the comparison of the two communities supports the thesis that sections in close proximity to one another and both dominated by Chenopodiaceae, under nearly identical conditions of altitude, soil, climate, etc., may differ enormously in regard to certain species.

Comparison of the Winslow-Holbrook section with other survey points along the Santa Fe Trail indicates the absence in these areas of the two dominant Atriplexes in Needles; the complete absence in Needles of those especially emphasized in this survey; and the secondary to minor position occupied by *Salsola kali* as compared to its dominance of the total vegetation in Seligman. The survey of the next point eastward, Gallup, New Mexico, will bring out the wide distribution of a true sagebrush entirely absent from communities above mentioned, and the increased importance of several members of the Chenopodiaceae.

CONCLUSIONS

1. The vegetation to be considered in pollinosis in this alluvial plains plateau predominantly belongs to the family Chenopodiaceae.

2. Attention is called to the potential importance of several species

not heretofore emphasized. Among the most significant of these are *Atriplex confertifolia, A. jonesii, A. powellii, Chenopodium incanum,* and *C. leptophyllum.*

3. The phenomenon of wide distribution of each of several species, within a relatively small area and near absence in the remainder of the community, has been established.

4. Pollinosis in either of these two towns could not be dismissed with the consideration of but one species, even though it be one of the most prominent.

5. The possible significance of typical western grasses has not been overlooked; although their importance is undoubtedly secondary to the Chenopodiaceae, even in the summer season.

6. A practical and inexpensive method for photographic representation of pressed specimens has been described. Several of the half-tones herein reproduced may be of aid in future taxonomic studies.

We are deeply appreciative of the assistance rendered us by several of the Santa Fe employees, and particularly by Mr. Edward Clark, trustee of the Santa Fe Coast Lines Hospital Association. The photographs of the plants were taken by Mr. I. F. Craig.

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STUDIES IN THE ASTHMATIC STATE*

II. The Reaction

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In a previous paper concerning a study of the stimulus to the asthmatic state[1] it was concluded that the manifestations of bronchial asthma, when once established, might result from any one of three classes of stimuli: (1) specific allergic or atopic stimuli; (2) infectious and irritative foci, involving the respiratory tract; and (3) a group of nonspecific excitants including atmospheric conditions, psychoemotional states, exercise, irritants, fatigue, as well as digestive, uterine and other functional disorders. Moreover, it was felt that the importance of various unrelated stimuli to the asthmatic attack pointed to an underlying constitutional basis of reactivity. The present paper is based on a study and consideration of the asthmatic response of patients whose stimuli have been carefully evaluated.

There is a wide variety in the intensity and character of the reaction in asthmatics. That the vagus nerve and its related branches exert immediate control over the reaction seems evident from the findings of numerous investigators and in particular from the results of the recent work of Kountz and Koenig[2] and Mount.[3] The complexity and wide range in the vagus control of the respiratory tract explain the great variety in the reactions that may comprise the asthmatic state. The typical asthmatic response consists in a contraction of the smooth musculature of the bronchial tract and a hypersecretion of the bronchial mucous glands with the typical symptoms of expiratory dyspnea, wheezing and cough. On the other hand, various degrees of these manifestations may occur; one of the most common of which is a limitation of the asthmatic response to cough, usually of the spasmodic type, and in children often mistaken for pertussis. The "cough reaction" is especially common in infants and children with adenoids and in adults with sinus disease; although, as will be shown later, it may follow any variety of suitable stimuli. A feeling of substernal tightness or pressure may be the only reaction of the underlying asthmatic state. This is especially common among hay fever sufferers at the height of the season. Sometimes this sensation is accompanied by cough. Again, the asthmatic response may consist in wheeziness only, without notable cough or dyspnea. An appreciation of the variability of the reaction in the asthmatic state is especially valuable in securing an early understanding of its underlying significance and thus

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inaugurating suitable measures of therapy before the full expression of the asthmatic response has occurred.

When the numerous reactions of the asthmatic state in respect to the various stimuli were analyzed in connection with the present study, it was found that, in general, no type of response was peculiar to any type of stimulus, and vice versa. For example, R. Z. is sensitive to ragweed pollen and orris root. She reacts to these atopic stimuli with tightness in the chest and wheezing. At times, when she has had a bronchitis, her asthma response is no different from that which occurs when she is exposed to those atopens. The same holds true, in her case, with other widely different varieties of stimuli, such as exposure to undue humidity, or an emotional upset. On the other hand, it is not true that every asthmatic reacts in the same way to every stimulus. M. S., aged seven years, is sensitive to tomato and strawberry. After the ingestion of these foods the child will cough, but this will be the full extent of her reaction. With respiratory infection and exposure to very humid weather she not only will cough but will complain of expiratory dyspnea, tightness in the chest and wheezing. J. H., aged twenty-three years, sensitive to ragweed, reacts to this pollen with tightness in the chest, wheezing and cough. At one time, not included in the ragweed season, while feeling perfectly well, she was exposed to sulphur fumes in a school laboratory. The result was an attack of asthma much more severe than any occurring in the ragweed season. W. C., subject to ragweed hay fever and asthma previous to hyposensitization, during the ragweed season, would have very severe paroxysms of asthma characterized by extreme dyspnea, wheezing and cough. With the passing of ragweed pollen from the air her attacks would disappear. However, during the winter on exposure to very cold air, she will cough and have wheezing, but in no degree comparable to the severity of her symptoms in the ragweed season. To summarize, the intensity of the stimulus together with the individual reactivity of the patient is of more importance than the kind of stimulus, in determining the quality of the asthmatic response.

A characteristic feature of the reaction, as studied, has been the generally diminishing severity that has occurred when one or more stimuli to attacks have been removed without completely eradicating the sum total of stimuli. M. D., aged forty-eight years, was very sensitive to orris root and stock dust. With elimination and desensitization she is able to encounter respiratory irritants with very little trouble; whereas formerly she would have a feeling of smothering and shortness of breath. Another patient whose asthma was associated with infected antra and sensitivity to orris root reacted very little to orris root exposure after the sinus condition was improved. J. W. reacted to cat dander and timothy grass pollen. The only time she had trouble with cat hair was during the pollen season. Likewise, it is true that since she has gotten rid of her cats she does not have so much trouble with pollens. It may be stated,

as a general principle, that considering the three classes of stimuli previously mentioned, the elimination of any one set, whether it be atopic, infective, or some of the miscellaneous group, will result in less reactivity to any of the remaining stimuli. This fact is of considerable use in the therapeutics of bronchial asthma and explains the helpfulness of history taking and diagnostic procedures that try to uncover the whole gamut of stimuli to the asthmatic response in each individual.

The character of the reaction in the asthmatic state is colored by the amount and kind of organic changes that have taken place. Thus, with chronic bronchitis and bronchiectasis, the cough, expectoration and wheezing often shade into the asthmatic reaction. Likewise, with emphysema and myocardial weakness, the dyspnea and orthopnea present between attacks predispose the patient to real asthmatic paroxysms. A knowledge of the underlying presence of these chronic conditions is very valuable in attributing the symptoms to their true origin.

When the asthmatic state is studied from the standpoint of its stimuli and reactions, it is clear that it is essentially a complicated reflex and necessitates for its understanding a knowledge of the general principles of reflex action. The general principles enumerated by Sherrington[4] several years ago are conformed to in the foregoing discussion of the asthmatic response. The wide variety in the stimuli to the asthmatic response is due to the wide receptive field of vagus innervation. The variability of the reaction is dependent, likewise, upon the fact that while the whole motor center of the vagus nerve potentially belongs to all and each of the groups of receptor organs proper to the reflex, the complicated efferent distribution of the vagus allows for a wide variety of motor phenomena in connection with the reflex.

While the nervous physiology of the asthmatic response is very important, the phenomenon of allergy so closely connected with the asthmatic syndrome has been difficult to fit into the picture of asthma as a neurosis. Here we have the problem of the interrelation of nervous and chemical mechanisms. W. Langdon Brown[5] has recently commented upon this difficulty by recalling the work of Lewis[6] on the skin reaction which showed that the "flare" depends upon the integrity of the sensory nerve fibers in the neighborhood, and the work of Langly which showed that the cells in the adrenal medulla that produce epinephrin are those which in the sympathetic ganglia form the postganglionic fibers. The work of Cannon[7] along these lines, in this country, also affords examples of the relationship between psychoemotional states and glandular activities with their chemical elaborations. A tempting hypothesis is that an inherited abnormal nervous reactivity is the reason for the tendency to atopic sensitivity.

At the present time, the therapeutic means to combat the asthmatic state at our disposal consist in the elimination of as many stimuli as possible, in hyposensitization for the atopic stimuli whenever feasible, in

eradication of foci of infection, and in measures designed to increase the stability and to reduce the irritability of the nervous system. The employment of these means frequently results in considerable benefit to the asthmatic. On the other hand, spontaneous remissions may occur without any particular therapeutic endeavor. A pressing question is what has happened in these individuals, for the core of the therapeutic problem is how to restore the constitutional reactivity to normal.

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BRONCHOSCOPY IN ASTHMA*

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AS HAS been recently emphasized,[3] to limit study of the asthmatic patient to an allergic investigation, to examination of the nose and throat, to a search for foci, or to a roentgenogram of the thorax, is to invite diagnostic and therapeutic failure. Study of the patient suffering from asthma should begin with a careful history and a general examination, which should be supplemented by such special examinations as each case may demand. With the introduction of bronchoscopy, still another important diagnostic and therapeutic aid is available, which, although infrequently necessary, has no substitute in certain cases of asthma.

To illustrate the value of bronchoscopy to the internist and allergist in certain cases of asthma the following two cases are cited.

REPORT OF CASES

CASE 1.—A man, aged forty-three years, a candy manufacturer and salesman, complained of persistent cough and asthma for six months. During the previous fifteen years he had had winter bronchitis with paroxysmal cough, productive usually of clear mucus. There never had been associated fever or hemoptysis. With the onset of warm weather each year he had been relieved of thoracic symptoms, until the summer previous to his admission to the clinic. Then cough, wheezing and dyspnea had developed which, probably because of the uncontrolled cough, had not been relieved by the usual antiasthmatic measures. Inhaled steam gave him his greatest temporary relief. Sometimes, after severe bouts of coughing, he brought up tenacious, rubbery, or stringy sputum. There was no family or personal history of other allergic conditions, and skin tests to air-borne and ingested substances gave negative results. The nose contained a few small, nonobstructing polyps, and roentgenograms of the sinuses were negative. Examination of the thorax on two successive days gave evidence of less expansion of the left lung than of the right, with a definite respiratory lag on the left side. Although asthmatic wheezing was present throughout both lungs, there was definite reduction in breath sounds at the left base posteriorly, associated with slight diminution of the percussion note. The findings in the thorax suggested, therefore, obstruction of the bronchus of the lower left lobe. The roentgenogram of the thorax was essentially negative.

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At bronchoscopy, the bronchi on the left side were found to be somewhat smaller than normal and to contain a moderate amount of serous secretion. This was aspirated. There was no evidence of organic bronchial obstruction. After bronchoscopy the thorax was examined with the stethoscope, and air was heard to pass freely into the left side. Although the patient was not entirely freed of symptoms by bronchoscopy, he was able to sleep without being propped in bed with pillows, and in other respects he was symptomatically much improved. He was advised with regard to the usual general measures for asthmatic bronchitis at the time of his dismissal.

CASE 2.—A housewife, a widow, aged sixty-three years, was admitted to the clinic January 21, 1931, and because of the severity of her asthma, was hospitalized at once. No family history of allergic disease could be elicited. Her previous medical history was essentially negative except that a "sinus operation" had been performed five years previously. She had considered her health excellent until June, 1929, at which time a cough developed and she gradually lost weight. The cough persisted through the winter, and in March, 1930, she experienced her first attack of asthma. Although the severity varied, she had almost constant asthma from March, 1930, to the time of her admission to the clinic. She had been thoroughly investigated from the allergic standpoint and treated by a competent allergist on two occasions elsewhere. The two or three months preceding her admission to the clinic were marked by constant and increasingly severe asthma. It was necessary for her to sit up in bed all day and all night. Epinephrine, ephedrine, and morphine administered repeatedly gave little temporary relief. Iodides had been given a thorough trial without appreciable benefit.

On admission at the clinic the patient was unable to walk; there was marked dyspnea, marked emphysema, the thorax was full of wheezing râles, and breathing was labored, calling into use every accessory muscle of respiration. She had lost weight markedly. Stereoscopic roentgenograms of the thorax disclosed a small region of old, fibrous tuberculosis of the right apex, and a region suggestive of bronchiectasis from the roentgenologic standpoint at the level of the third, fourth, fifth, and sixth ribs anteriorly on the left. The cough, although hard and rasping, was for the most part dry. Rarely could the patient raise any sputum in spite of desperate attempts to do so. On the second day in hospital, the patient for the first time raised a small amount of bright blood after hard coughing.

The usual symptomatic remedies were almost futile. Epinephrine in doses of 7 to 15 minims was used frequently, with little if any temporary benefits. Morphine, grain ¼ (0.015 gm.), given hypodermically, was necessary once or twice daily to give the patient rest. An iodide antiasthmatic mixture was given three to six times daily without the usual beneficial effects. No apparent increase in secretion or liquefaction of mucus

from the bronchi was observed. Inhalations of steam were likewise of little benefit. Although there was nothing in the thorax to suggest localized bronchial obstruction, the progressive downhill course in spite of usually adequate therapeutic measures, and the region suggestive roentgenologically of bronchiectasis in the left anterior part of the thorax, together with the recent appearance of bright blood in the sputum, made bronchoscopy advisable.

Eight days after admission, therefore, bronchoscopy was performed. The trachea and bronchi were found to be lined with a large amount of very thick, gelatinous, membranous-like secretion which was difficult to remove by suction. There was no evidence of bronchiectasis and nothing to suggest neoplasm. Following bronchoscopy the patient was able to lie flat in bed, and slept all night without coughing. Not much sputum was raised following bronchoscopy. Two days later, the patient was dismissed and she returned to her home in Texas. She was comfortable, and examination of the thorax was negative except for a few mild wheezing râles.

In November, 1932, twenty-two months after the patient's previous admission, she came to the clinic again for relief of asthma, with the following history. After her return home she got along fairly well, having an occasional mild attack of asthma usually precipitated by smoke or north winds and easily controlled by the use of iodides or by inhaling the smoke of powders for asthma. However, two weeks before her return to the clinic, the house of a neighbor caught fire, the wind blowing smoke and sparks into the patient's yard. A cough developed, and later a cold, followed by rather severe asthma, the patient having four to six severe paroxysms daily, lasting one to three hours each. She coughed much and expectorated some clear mucus. Between paroxysms she could lie flat in bed comfortably. The recent medication at home had consisted chiefly of digitalis and also morphine given hypodermically two or three times daily in doses of ½ grain (0.032 gm.).

On admission to the clinic the patient was having moderately severe asthma, with considerable emphysema. Asthmatic râles were present throughout both lungs; there was no evidence clinically of bronchial obstruction. Between paroxysms of asthma there was practically no wheezing or discomfort. Because of the remarkable relief obtained from the asthmatic symptoms by the previous bronchoscopy, the patient came with the expressed purpose of having the procedure repeated. Although we did not expect her to obtain much relief from bronchoscopy under the circumstances existing on the latter visit, we acceded to her wishes.

Five days after the patient's second admission to the clinic, bronchoscopy was performed, at which time a little congestion of the bronchi was noted, as well as a small amount of thin secretion. The results of the procedure were equally as effective as on the previous visit. The asthma practically ceased, and it was possible for the patient again to lie flat in bed and to sleep uninterruptedly. Asthma did not return in spite of

a severe nervous shock, including death and illness in the family, which necessitated a sudden trip to Texas the day following bronchoscopy. In subsequent letters, the patient has stated that her condition remains good, that she is having little asthma, and that it is easily controlled by iodides.

DISCUSSION

The bronchoscopic findings in cases in which there are asthmatic symptoms vary considerably, and should be considered from the standpoint of the findings in bronchial asthma and the findings in other conditions accompanied by asthmatic symptoms. In the interval between paroxysms of bronchial asthma the membranes usually have a fairly normal appearance, whereas during attacks redness and swelling,[11] rhythmic contraction of the bronchi with congestion and swelling,[7] redness and edema,[4] purplish mucosa and bronchi filled with secretions,[6] urticarial patches,[8] spasmodic stenosis simulating cicatricial stenosis,[5] collapse of the trachea during expiration,[1, 8, 10] and catarrhal tracheobronchitis[8] with exudate similar to that noted in our second case, have been described. The absence of true bronchial spasm in all reports is noteworthy. The other group of patients having asthmatic symptoms rather than true bronchial asthma present a wider range of bronchoscopic findings usually dependent on the type of lesion underlying the symptoms. In this group of cases will be those in which there is chronic suppurative tracheobronchitis, bronchiectasis, pulmonary abscess, foreign bodies, ulcerations, scars, and primary malignancy of the tracheobronchial tree. In the latter group the indications for bronchoscopy are usually clear cut. In the former group, bronchoscopy is rarely necessary and the indications are less distinct. Close cooperation between the internist and the bronchoscopist in the selection of cases for bronchoscopy is necessary.

Bronchoscopy in the first case was indicated to rule out the presence of an organic bronchial obstruction as the cause of the patient's asthmatic symptoms, and of the findings typical of obstruction in the left base posteriorly. The value of bronchoscopy under these circumstances cannot be overemphasized. Of seventy-one cases of primary carcinoma of the bronchus reported by Vinson, bronchostenosis was present in fifty-three cases and was the most frequently observed physical sign. Whether the obstruction in the case in question was due to secretions blocking the bronchi or to a more serious malignant or benign lesion could be settled in only one of two ways. The first method, observation over a long period of time during which the patient would have symptomatic treatment for the asthmatic bronchitis, was not followed because of the limited time the patient could remain at the clinic and because prolonged delay is not justifiable in any case of bronchial obstruction of undetermined cause. The method of choice is bronchoscopy, which at once settles the diagnosis.

The relief of asthmatic symptoms following bronchoscopy has been

noted in many instances of asthmatic bronchitis both in this clinic and elsewhere. However, regardless of the relief obtained, bronchoscopy is indicated in any case of asthma in which physical signs of bronchial obstruction exist. Occasionally one sees small or large casts of portions of the bronchial tree, which produce signs of bronchial obstruction. These usually are raised by coughing, but occasionally the use of the bronchoscope is necessary for their removal. It is of considerable historic interest to read the account of Tulp, who, in 1716, described "an entire vein cast up from the lungs" by coughing. He declared this bronchial cast to have been the size of two hands. Similarly, Warren in 1767, described two large "bronchial polyps" or casts raised from the thorax after severe prolonged coughing. The cases more recently described as instances of acute and chronic fibrinous bronchitis, which one occasionally sees, are similar to those just mentioned, in that they produce casts of the bronchi and bronchial obstruction. A patient seen recently by Maytum, and who was subjected to bronchoscopy because of clinical signs of bronchial obstruction, was found to have a large fibrinous cast of the bronchi which was removed, with relief of symptoms. With the same physical findings, however, it is more common to find bronchostenosis due to more serious disease. Only too frequently does the bronchoscopist encounter cases erroneously diagnosed as bronchial asthma when in reality bronchostenosis due to organic disease exists.

In the second case reported, bronchoscopy was carried out the first time because the asthmatic symptoms were of long duration, the patient was becoming progressively worse in spite of usually adequate medical measures, there had been recent hemoptysis, and, the roentgenologic findings suggested a localized area of bronchiectasis. The finding of thick, tenacious, gelatinous exudate lining the bronchi and trachea, and materially narrowing the lumen of the tracheobronchial tree in this case, has been noted on previous occasions here and elsewhere.[1, 6, 8, 10, 12, 13, 17, 18] As long ago as 1679, Willis, in writing on the production of asthmatic symptoms by various means, mentioned among other causes "thick humors and viscous, or purulent matter or blood extravasated," or "little swellings, or Schirrus's, or little Stones," or finally that "a catarrh of a serous humor suddenly distills upon them." It seems quite certain that Willis was describing an exudate not unlike that encountered in our case. The removal of such exudate gives remarkable relief of symptoms of varying duration. The dryness and tenacity of this false membranous exudate in the trachea and bronchi in such cases explain the comparative lack of sputum and the futility of the hard, racking cough. To permit the patient to persist in coughing in an attempt to dislodge this material only aggravates the asthma, and prolongs the labored mouth-breathing which, in turn, drys the mucous lining even more and thus creates a vicious cycle which, if unrelieved, could conceivably terminate in exhaustion and death. The ineffectiveness of iodides and other medication in such cases

is unexplained. Certainly adequate doses of iodides were administered both before and after the patient's coming to the clinic, without in any way liquefying the mucous material previously excreted and adherent to the mucous membrane. It is possible that the iodides were administered too late to be effective. Had they been used before this dry, tenacious membrane of mucus had formed, the excreted mucus possibly would have been of more liquid consistence and no real difficulty in raising excess mucus would have occurred. Certainly the patient's asthma was very favorably affected by the subsequent occasional use of iodides, and at the time of her second bronchoscopy no tendency to form a dry, tenacious exudate was noted. Iodides continue to benefit this patient, being practically the only medication she uses; in fact, they are so effective in her case that we have to warn her not to use them when they are not necessary.

Removal of secretions plastered over the tracheobronchial tree accomplishes several things. In addition to relieving more or less obstruction to the lower air passages and thus restoring the mucous membrane to more normal function, removal of the exudate eliminates many of the bacteria and their products from the tracheobronchial tree. That this removal of bacteria may be of definite clinical benefit is supported by the studies of Ramirez and St. George on the comparative effectiveness of vaccines made from organisms obtained from the sputum and those obtained from the bronchial secretions direct. They found that "in a considerable number of patients the bronchial culture showed a single organism—usually the Micrococcus catarrhalis—whereas the sputum culture generally showed mixed cultures, no doubt due to oral contamination. Vaccines thus obtained from the bronchi gave greater relief than the usual sputum cultures." In bacterial studies carried out by Weille, however, in the majority of cases there was more than one organism in cultures from the bronchi, and the diversity of organisms found led him to feel that no single bacterium is characteristic in these cases. Furthermore, "no relationship between the presence or absence of organisms and the clinical improvement of the patient following bronchoscopic treatment could be observed." In our cases the relief which so quickly followed bronchoscopy seems best explained by the mechanical relief of obstruction, or the sudden breaking into the reflex asthmatic cycle, rather than to the removal of bacterial or other toxic substances from the tracheobronchial tree.

It is not difficult to understand the relief of symptoms from bronchoscopy when partially obstructing secretions are removed from the trachea and the larger bronchi. This is the most likely explanation for the relief obtained in the second case, when bronchoscopy was carried out the first time. Since practically no secretions were removed when this patient was subjected to bronchoscopy the second time, other factors must have played a part in the relief of her symptoms. In the first case, also, the relief

obtained following bronchoscopy was out of proportion to the amount of secretions removed. The effect of local anesthesia in the pharynx, larynx and trachea is no doubt of temporary benefit. In our cases a 20 per cent solution of cocaine is used to swab the pharynx and larynx, and a 5 per cent solution of cocaine is instilled later into the trachea before bronchoscopy. The effect of local anesthesia is transient, however, and wears off long before the patient has recurrence of asthmatic symptoms, so that still other factors are doubtless involved. In this connection it is interesting that Freudenthal, while performing bronchoscopy on a patient in an interval between attacks of asthma, observed a scar-like mass obstructing the entire lumen of a bronchus. This mass disappeared following application of 20 per cent cocaine and, on subsequent bronchoscopy, he saw no evidence of this abnormality.

The psychic effect of bronchoscopy on the asthmatic patient also is probably of some importance in relief of symptoms after bronchoscopy. Lukens reported the experience of Clerf in producing an apparent cure after a single passage of the bronchoscope without any other treatment. In this instance he felt that the symptoms were of neurotic origin. The appraisal of the importance of the psychic effect of bronchoscopy is difficult and is dependent chiefly on ruling out any other factors which contribute to the patient's symptomatic relief. Too many different factors are at work to allow each one to be weighed accurately; the relief obtained is doubtless a summation of several factors.

On the whole, the greatest benefit from bronchoscopy in asthma is to be expected in cases of asthmatic bronchitis, in which old, dry secretions cause some mechanical narrowing or obstruction of the lumen. The character and distribution of this secretion is of more importance than the amount, inasmuch as a very small amount, not dislodged by coughing, can grossly obstruct several large bronchi.[17]

The value of bronchoscopy as a diagnostic and therapeutic aid in certain cases of asthma is well illustrated in the two cases reported. Let us emphasize again, however, that bronchoscopy is infrequently necessary in asthma, but under certain circumstances no substitute for its intelligent use is to be found. The need for close cooperation between the internist or allergist and the bronchoscopist in the care of such cases cannot be overemphasized.

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THE RELATIONSHIP OF SO-CALLED STATUS THYMICO-LYMPHATICUS TO ALLERGY

(Based on an Autopsy Study of 38 Cases)

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AN EDITORIAL of the *Journal of the American Medical Association* has recently designated the problem of so-called status thymico-lymphaticus a "sphynx like mystery."[1] Most recent contributors to the literature on so-called thymic death are indeed at a complete loss to explain this phenomenon. Very painstaking research of recent years has led to but few positive observations. The work of the English Status Lymphaticus Investigation Committee[2] on over 600 autopsies tends to question the existence of a thymic diathesis. The diagnosis of thymic death is frequently made the dumping ground of unexplained sudden death (Kennedy and New[3]). Thymic enlargement is often diagnosed erroneously on insufficient roentgenographic evidence (Hasley and Di Tomasi[4]). Boyd[5] observed that a large thymus is rather the rule than the exception in patients dying suddenly. The formerly prevalent conception that pressure upon the thymus is responsible for the production of so-called "thymic" asthma and even for death has lost considerable ground within recent years.

In spite of these various observations tending to deny the original conception of Paltauf that a large thymus is instrumental in causing sudden death, the fact remains that there are patients with hyperplastic lymphoid tissue who die suddenly and in whom the autopsy findings do not give any clue whatsoever to the cause of death. Various reasons have suggested to me a close relationship of the allergic state with what has been called the thymico-lymphatic constitution and have brought up the question of whether or not the mechanism of death in these cases may not be quite similar to, if not identical with, that of human anaphylactic shock as it is observed following injections of serum, pollen, and other antigens. The reasons for this conception are the following:

(1) Thymus in anaphylactic shock: Among 15 cases of anaphylactic shock following serum injections reported in the literature, eight were reported to have had enlargement of lymphoid structures (Waldbott[6]).

(2) Thymus in asthma: In a recent report of eight asthmatic deaths by MacDonald[7] enlargement of the thymus and lymphoid structures was recorded in all cases. Others (Huber and Koessler[8]) have noted such changes in connection with asthmatic death, although they have not emphasized these lesions in their reports.

(3) Thymus in sudden death following administration of drugs: Of 20 autopsied cases of sudden death following administration of local anesthesia reported by various pathologists, thymic hyperplasia was present in eleven (Mayer[9]). Jaffe[10] reported that of 26 cases of sudden death during general anesthesia, 10 had thymic and lymphoid hyperplasia. For the past three years I have been looking for instances of sensitization to cocaine, novocaine and ether among my allergic patients. I have recently been able to report five such cases of respiratory sensitization.[11]

(4) Thymus in allergic children: In a number of my allergic patients whose asthma began immediately after birth, the diagnosis of "thymic asthma" had been made by their physicians because of x-ray evidence of enlarged thymus. While it is difficult to make such a diagnosis on the basis of single x-ray examinations,[4] Tumpeer[21] concludes as the result of a thorough follow-up of 38 children combined with repeated fluoroscopic examinations, that there exists a relationship of infantile allergy with hyperplasia of the thymus and the other lymphoid organs.

(5) Sudden death in allergic families: I have records of members of several asthmatic families who have died suddenly from minor causes similar to the way in which patients die from "thymic death." For example: a six-year-old son of a hay fever patient died during tonsillectomy soon after the induction of general anesthesia. A three-year-old child of an asthmatic patient died suddenly during a minor upper respiratory infection. The newborn baby of a hay fever patient developed asthma-like symptoms which lasted for several weeks and then suddenly terminated fatally; the autopsy revealed enlargement of thymus and lymphoid structures. An asthmatic adult died during a minor nasal operation without apparent cause.

(6) "Thymic" and allergic constitution: In studying the characteristic features of what has formerly been termed the thymico-lymphatic constitution, it is difficult to make a distinction from the manifestations of the allergic make-up. In fact, such symptoms as chronic upper respiratory catarrhs, gastrointestinal upsets, eczema, eosinophilia which have been associated with the thymico-lymphatic constitution by former clinicians (Waldbott and Anthony[13]) are now definitely regarded as allergic.

While none of these facts are in any way conclusive, they were nevertheless sufficient to stimulate investigation into the possible association of status thymico-lymphaticus with status asthmaticus and the relationship of "thymic" death to anaphylactic death.

In determining satisfactory methods either to prove or to disprove this relationship one encounters great difficulties. The diagnosis of status lymphaticus usually cannot be definitely established before death, and after death clinical and immunologic investigation is impossible. When one attempts to study the reported pathologic condition of thymic death

and make comparisons with the pathologic changes seen in human anaphylaxis, one again encounters difficulties because the literature records very few thoroughly described cases of anaphylactic death. I, therefore, decided to accumulate as much data as possible on the clinical, pathologic and immunologic factors underlying human anaphylactic shock. In the following it is attempted to apply this experience to a study of "thymic death."

Although there are certain reasons for a distinction between anaphylactic and allergic shock in man, many are inclined to consider both types of shock as identical. For reasons outlined elsewhere[14] the differentiation between anaphylactic and allergic shock, if justified at all, is of little importance to the clinician and is therefore not applied to this study.

HUMAN ANAPHYLAXIS

Probably the most characteristic symptoms of human anaphylaxis occur when an overdose of pollen extract is given (Waldbott[15]). Its mechanism is dependent on three factors: (1) the degree of individual sensitivity, (2) an overdose above the patient's tolerance, and (3) the rate of absorption. Factors contributing to the effect of an overdose are incomplete absorption of an injection previously given, absorption of additional pollen through the nose as encountered during the pollen season, and absorption through the gastrointestinal tract of substances other than pollen to which the patient is sensitive. An overdose may, therefore, be brought about not only by one antigen absorbed in one manner but by a multiplicity of causative agents, either injected, inhaled or absorbed through the gastrointestinal tract. During the course of these studies on shock following pollen injections it was observed that the reaction was more severe and bore greater resemblance to the conditions in the experiment with the anaphylactic animal in a degree proportionate to the size of the overdose, the rate of absorption and the patient's degree of sensitivity. When the absorption was slowed down and the overdose was not considerably in excess, any or most of the known allergic manifestations appeared during the course of the shock.

In a subsequent analysis of eight cases of anaphylactic death[6] following injections of horse serum, the records of which were placed at my disposal, it was found that there is essentially no difference in the mechanism and the symptomatology of shock as compared with reactions due to pollen injections.

In a recent paper[14] I dealt with a series of reactions following injections of substances other than pollen and serum. A fact well known to many was demonstrated; namely, that injections of such antigens as drugs, foods, extracts of bacteria and fungi are liable to produce symptoms identical with those seen after pollen injections. After an intravenous injection of sodium iodide in one case and urethan-quinine in another, the same symptoms of anaphylactic shock as those which are observed

following pollen and serum injections occurred. Again it was shown that a violent allergic reaction and protracted anaphylactic shock cannot be differentiated clinically. Furthermore, it was demonstrated that typical shock may be elicited in ways other than by injections. An additional factor in the production of shock was emphasized; the time interval between two injections may under certain conditions greatly enhance the degree of sensitization. This again is in accord with the observations in animal experiments in which the interval between the sensitizing and shocking dose is of greatest importance.

The clinical and pathologic manifestations of anaphylactic shock are subject to great variations. Perusal of the available literature indicates that the chief pathologic lesions are capillary congestion and edema with subsequent cellular infiltration. These lesions have been excellently described by Kline and coworkers[16] in their investigation on the allergic wheal. Recent experiments by Szauter and Roth[17] revealed the following: If the antigen is introduced into the venous system, the capillary circulation of the lungs, which are then first reached by the antigen, becomes principally involved by these changes as clinically evidenced by the symptoms of wheezing and dyspnea. Because absorption from an injection takes place almost entirely through the lymph and venous system, the predominance of pulmonary symptoms in anaphylaxis can thus be well understood. If the injection is given into the carotid artery, the edema occurs in the brain, and convulsions and other cerebral symptoms manifest themselves. If the injection is made into the portal vein, the clinical syndrome of collapse and changes in the liver function is most pronounced. This great variability of the symptoms of anaphylaxis is further enhanced when a previous allergic lesion is present (Waldbott[15]). The administration of the antigen usually tends to flare up such a lesion. For example, in a case of allergic migraine headaches cerebral symptoms were produced by an overdose of antigen. In a pollen sensitive patient with gastrointestinal allergy, an overdose of pollen elicited gastrointestinal spasm, pain, and vomiting. Thus, the typical picture of human shock becomes further clouded. In addition, the rapidity of absorption of the antigen is liable to modify the symptoms, inasmuch as in intravenous injections death may appear so rapidly that no symptoms whatsoever can be noted (Duke[18] and Lamson[19]).

PATHOLOGY OF SO-CALLED THYMIC DEATH

With these facts in mind, 102 cases of so-called "thymic death" were studied. One is confronted with the question of what justifies the diagnosis of "thymic death." The work of Young and Turnbull,[2] Hamar[20] and particularly of Boyd[5] indicates that an "enlarged thymus" is frequently present in any type of sudden death regardless of the cause. In the following, therefore, reliance has been placed less upon the degree of enlargement of the thymus, the interpretation of which may be subject

to the personal equation, than upon the simultaneous presence of a general lymphoid constitution and the absence of any definite lesion to account for death. Of a total of 102 cases, 68 were eliminated because various conditions were found the presence of which was an adequate cause of death. Thus, this study differs essentially from that of the English Status Lymphaticus Investigation Committee, the work of which included all such cases.

The 34 remaining cases were grouped into three classes: (1) Those in which, aside from the typical lesions to be described below, no other contributing incident as cause of death could be determined; (2) those in which minor usually nonfatal ailments were associated and death ensued; (3) cases in which the patients developed clinically a syndrome of dyspnea, stridor, fever and collapse for several hours or days before death occurred. The pathologic findings were quite similar in all three groups. The development of the above mentioned syndrome in the third group can probably be considered as a part of the whole clinical picture in those cases in which the illness did not terminate immediately after the onset.

AUTOPSY FINDINGS

The most outstanding finding in the 34 cases, the details of which have been presented elsewhere,[21] was the presence of typical lesions in the lungs, characterized by capillary congestion and edema. The lesions varied in size and degree of development. In some areas there was capillary dilatation, in others extravasation of blood cells and edema fluid through the capillary walls. In the most advanced lesions there was complete destruction of lung tissue by the edema. In some there was a tendency of organization of this edema by immigration of lymph cells, leucocytes and eosinophils. In another group the clinical picture of bronchopneumonia had arisen before death, and areas resembling those of bronchopneumonia were present. There were also areas of emphysema and atelectasis. In none of these cases were there sufficient pathologic changes of the heart and kidneys to which the origin of edema is usually attributed. It is true that in some in which the pulmonary lesions were greatly advanced, a more or less marked dilatation of the right heart was found. However, because this occurred only in 14 of 34 cases and because the degree of dilatation appeared to be dependent upon the extent of the pulmonary changes, I believe that this condition of the heart is secondary to the congestion in the pulmonary circulation; the right heart becomes insufficient in overcoming the additional burden in the capillaries of the lungs. There were in a few cases pronounced edema in other parts of the body, particularly in meninges, kidneys, lymph tissue, etc.; but this was not a uniform finding. In some cases degenerative changes in the liver and kidneys were found.

The presence of the pulmonary edema has undoubtedly been noted by other investigators. They considered it as evidence of passive congestion

and for this reason have not emphasized its presence. However, there is reason to believe that this edema is the primary cause of death. Aside from its constant appearance there were in 29 cases numerous petechial hemorrhages of various organs which indicate that the patients died from asphyxiation. No evidence of obstruction of air passages other than the pulmonary edema was found. Congestive changes were also present in other organs, but these lesions were not of constant occurrence.

The following reasons indicate that this edema may be considered as an anaphylactic allergic lesion.

1. The lung findings resemble very closely those which are described and illustrated by Dean in his classical report of a case of anaphylactic death following a prophylactic injection of tetanus serum. With the exception of a few others, in most subsequent reports on anaphylactic death the description of the microscopic findings is either little exhaustive or the picture of shock is clouded by such additional diseases as pneumonia, diphtheria, asthma, etc. Dean has also drawn attention to congestive and degenerative changes in the liver, the similarity of which with the above mentioned findings is very striking.

2. In 9 of 13 cases in which a satisfactory history could be obtained there was evidence of previous allergic conditions in either the patient or his family. Most of these autopsies were done several years ago and only few data regarding the history were recorded because of the suddenness of the accidents.

3. In 13 of the 34 autopsied cases there was an unusual number of eosinophils in the lungs, in the gastrointestinal tract and in the blood of the distended capillaries.

4. A clinical investigation with Dr. Anthony[13] of Children's Hospital of Detroit, in which 30 children were followed up who had formerly been treated with x-ray over the thymus gland, revealed that all but 5 were allergic, as determined by skin tests, personal and family history. In 3 of these 5 cases sensitization was suggested but not definitely proved.

As a fifth, although not as conclusive, reason for the close relationship of these pulmonary lesions with allergy, I wish to point to certain changes in the adrenals, particularly to the hypoplasia of the medulla which was present in 18 cases. Jaffe[22] and Marine[23] demonstrated that there is a distinct correlation of adrenal pathologic conditions and lymphoid hyperplasia. In view of the well known effect of epinephrin, the product of the medulla, upon the allergic wheal, this fact is of interest. The relationship of adrenal pathologic condition with asthma is, however, if it exists at all, very uncertain.

ABSORPTION OF ANTIGEN

It was, of course, impossible to determine the causative antigens which induced death in the various patients. However, I believe from my previous observations on human anaphylaxis, that any food, pollen, serum,

bacterial substance, local or general anesthetic, or any other drug, may act as such an antigen. In regard to the mode of absorption, it can be recalled that especially in children the gastrointestinal tract is unusually permeable. Walzer[24] has definitely shown that undigested food enters the blood stream through the intestinal tract. Absorption of whole antigen may take place through the nose and upper respiratory tree, as shown by Cohen and coworkers[25] with regard to pollen, by Ratner et al.[26] for other antigens. Anthony and I have brought out[13] that in one of the series of 30 children severe shock occurred after a scratch test with walnut. Only the epidermis was scarified, no blood being drawn. The edema began at the site of the test and spread within two minutes throughout the body, followed by asthma and edema of the upper respiratory organs. This mode of production of shock points to absorption of antigen from the excoriated epidermis. It was definitely stated by the mother that this child, a breast-fed baby, had never had occasion to eat walnut before. Thus, the question arises whether or not the contact with and absorption of food in young children for which reagins have been transmitted either through the placenta or with the breast milk from the mother may be responsible for the frequency of this accident in children (Ratner et al.[27]). One of the most unusual cases of my series is the sudden collapse and subsequent death of a thirty-seven-year-old woman who had been suffering for three months from mucous colitis, an allergic condition. In addition to the pulmonary manifestations which were indicative of anaphylactic shock, the mode of death suggested this diagnosis because of the before mentioned observation that in anaphylaxis an overdose of an antigen produces a flare-up of a previously existing allergic condition in addition to the other anaphylactic changes. Thus the symptoms were suggestive of allergic abdominal spasm, pulmonary edema and possibly of glottis edema. The autopsy (Dr. P. F. Morse, Harper Hospital) showed marked spasm in the lower intestines, marked capillary congestion and edema of the lungs, marked emphysema and petechial hemorrhages in various organs. There was a marked hyperplasia of the thymus and of the lymphoid organs. There were also the characteristic diminution of adrenal substance as noted by other investigators; in this case it was brought on by a chronic inflammatory process.

I am not able to go into the various interesting associations of the lymphoid system with allergy. The bad effect of removal of lymphoid tissue, such as a tonsillectomy, upon asthmatic patients is well known to clinicians. The lymph glands are closely associated with elimination of eosinophil cells from tissues and blood stream (Biggart[28]). Their rôle of combating foreign material, particularly bacterial infection, is well established. The presence of exhaustion and necrosis of lymphoid germ centers induced Symmers[29] to assume that a toxic substance is deposited in lymph glands and the thymus. Hamar[20] suggested that the Hassall corpuscles may be the pathologic exponents of an antitoxic function of

the thymus. Whatever the facts may be, there appears to exist an intimate association of the lymphoid system with immunologic and allergic processes, the nature of which is not understood.

CONCLUSIONS

1. Of a group of 102 cases in which the diagnosis of status thymico-lymphaticus was made by various pathologists, 34 were selected in which no adequate cause of death had been determined. Sixty-eight cases were excluded, since other conditions such as hyperthyroidism, birth trauma, gastroenteritis, respiratory infections, etc., were associated with lymphoid hyperplasia, these in themselves being sufficient to cause death.

2. In 11 of the 34 cases death occurred without previous illness, nor were there any pathologic lesions to indicate the presence of a previous illness. In 16, minor usually nonfatal incidents preceded death. In 7, a syndrome developed manifesting dyspnea, stridor, fever and shock.

3. The lungs in all these cases presented uniform changes, characterized by capillary congestion, extravasation of blood cells and edematous fluid. These lesions alternated with areas of emphysema and atelectasis. In 17 cases petechial hemorrhages were present involving heart, pleura, lymph glands and various other viscera. In some, there were dilatation of the right heart and degenerative changes in the liver, and edema and capillary congestion in other organs than the lungs. Hypoplasia of the adrenals and hyperplasia of lymphoid organs as noted by other authors were present.

4. Comparison of this pathology with that reported on human anaphylactic shock reveals a close resemblance if not a complete identity of the two conditions. Tissue eosinophilia and an allergic family or personal history were observed.

5. On the basis of these findings it is believed that death may be the result of a primary anaphylactic edema of the lungs and ensuing asphyxiation. Such a theory can be upheld only if one assumes (1) that anaphylactic shock may occur from incorporation into the body of non-protein substances, and (2) that absorption of shock-producing antigen may take place by ways other than injections. On the basis of my own experience and that of others, these two possibilities are discussed.

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MIGRAINE*

Some Considerations of Allergy as a Factor in Familial Recurrent Headache

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THE relation of migraine to the allergic diseases suggested almost a century ago by Trousseau and others, has received much consideration during the past few years. While these studies, which have been reviewed by Vaughan[1] in 1927 and more recently by Rowe,[2] definitely establish the rôle of allergy as a cause of headache, allergy's relation to migraine is still an unsolved medical problem. These facts indicate the need of detailed and extended study of this subject in the migrainous patients, both as individuals and as groups. At this time it is possible to make a preliminary report of several such observations in the evaluation of the allergic factor in migraine.

TERMINOLOGY

The term "migraine" will be used in two ways in this paper: (a) to designate attacks of headache with cortical features, i. e., scintillating scotomata, hemianopia (homologous), motor aphasia and paresthesias; and (b) to refer to a clinical entity, i. e., recurrent paroxysmal headaches, familial in nature and for which no organic cause can be found.

Eyermann[3] in 1929 emphasized that the relationship of sensitization to headache was broader than to that of migraine, and it may be reemphasized, it is not broad enough to include all migraine. Headaches due to allergy are induced by inflammatory changes, pressure or toxemia, resulting from allergic reactions in the nose, sinuses and supposedly similar changes in other organs. The presenting symptoms are due to either the local (i. e., hypersecretion, exudation, pressure or functional disturbances) or systemic reaction of allergy (systemic effect of toxins produced at site of local reaction), and may be that of migraine or headaches without sensory, motor or vasomotor phenomena. The last mentioned group includes cases (a) without and (b) with demonstrable pathology of the nose and sinuses as well as (c) the headache of general allergic reaction (Duke[4]).

PRESENT VIEWS CONCERNING THE ROLE OF ALLERGY IN MIGRAINE

In the main, allergists today hold one of three views concerning the rôle of hypersensitiveness in migraine, namely: (1) *that there is no relation,* (2) *that migraine is an allergic (atopic) disease,* (3) *that sensitization is a factor in some cases.*

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Those who believe that allergy has no relation to migraine do not deny the specificity of certain allergens as a cause of headache, but contend there is a difference between the "migraine" attacks induced by these foods and the clinical entity, migraine (familial recurrent headache).

The hypothesis that migraine is an allergic (atopic) disease cannot be maintained, unless there is proof, not only that allergens are responsible for attacks, but also that the mechanism of symptom production is that of atopic hypersensitiveness. This premise is upheld by Coca's statement[5]: "Specific sensitiveness is an immunologic disease, to the understanding of which two keys are necessary. The first is the idea of the *specific mechanism* and the second is the idea of the *shock organ* (Doerr)."

While most workers concur with the third viewpoint, it appears that not sufficient time has elapsed since the original report of Vaughan to make any definite conclusions. Of those accepting hypersensitiveness as a primary cause of migraine, there are some who believe foods alone are etiologic, while others include inhalants as well.

I. STUDIES EVALUATING THE ALLERGIC FACTOR IN MIGRAINE

A. The History and Symptomatology

A detailed analysis has been made of the history and symptomatology of a series of patients with recurrent headache as a primary complaint, for the following purposes: (a) to determine whether headaches relieved by allergic therapy were those of true migraine, (b) as a means of establishing the clinical features of headaches due to sensitization, and (c) to learn whether one might be able to evaluate the probability of allergy in these patients from this analysis. For this study, I used a history form compiled from a number of standard texts dealing with migraine.[6]

CHART

I. GENERAL INFORMATION
- 1. Age of onset
- 2. Duration of attacks
  - a. Average
  - b. Extreme
- 3. Frequency per month
- 4. Recurrence
  - a. Periodic
  - b. Irregular
  - c. At menses only

II. THE PRODROMAL STAGE
- 1. Depression
  - a. Physical
  - b. Mental
- 2. Hyperactivity
  - a. Physical
  - b. Mental

3. Symptoms peculiar to the prodromal stage
   a. Bulimia
   b. Fetid breath
   c. Stomatitis
   d. Globus hystericus
   e. Urticaria
   f. Purpura
   g. Asthma
   h. Hay fever
   i. Abdominal distress
   j. Yawning
   k. Sleepiness
   l. Aching of neck muscles
   m. Soreness at angle of jaw

III. SENSORY, MOTOR AND VASOMOTOR SYMPTOMS

A. Sensory
   1. Loss of vision
      a. Hemianopia
         Homonymous
         Heteronymous
         Altitudinal
      b. Quadrantic blindness
      c. Transitory amaurosis
   2. Disturbances in visual function
      a. Scotomata
      b. Scintillating scotomata
      c. Blurring of vision
   3. Olfactory changes
      a. Anosmia
      b. Hyperosmia
      c. Parosmia
   4. Auditory changes
      a. Hyperacusis
      b. Hypacousis
      c. Paracusis
   5. Paresthesias
      a. Type
         (1) Unilateral
            (a) Homolateral
            (b) Contralateral
         (2) Bilateral
      b. Part affected
         (1) Scalp
         (2) Face
         (3) Tongue
         (4) Body
         (5) Extremities
         (6) Abortive forms

B. Motor symptoms (paresis or paralysis)
   1. Disturbances of oculomotor nerves (III, IV, VI)
      a. Diplopia
      b. Ptosis
      c. Strabismus

2. Extremities
   a. Unilateral
      (1) Homolateral
      (2) Contralateral
   b. Bilateral
3. Motor aphasia
4. Cerebellar ataxia
5. Agraphia

C. Vasomotor symptoms
1. Sympatheticotonic (white migraine)
   a. Pallor of affected side
   b. Temporal artery of high tension
   c. Lowered temperature on side
   d. Retraction of eye globe
   e. Mydriasis
2. Sympatheticoparalytic (red migraine)
   a. Redness of affected side
   b. Lacrimation
      (1) Unilateral
      (2) Bilateral
   c. Photophobia
   d. Contraction of pupil
   e. Elevation of temperature in affected area
   f. Unilateral hyperhidrosis
   g. Temporal artery distended
3. Sweating
   a. Location
   b. Duration
4. Coldness of extremities
5. Hemorrhages
   a. Melena
   b. Purpura

IV. THE ATTACK
1. The location
   a. Starts:
   b. Progresses to:
   c. Terminates at:
   d. Maximum intensity:
   e. Involves the following areas:
      (1) Frontal
      (2) Parietal
      (3) Occipital
      (4) Temporal
      (5) Vertex
2. The course of the pain
   a. Hemicrania
      (1) In all attacks
      (2) Occasionally
      (3) Alternating
      (4) Transmutation to bilateral
      (5) Crossed

b. Bilateral pain
(1) Every attack
(2) In part of the attacks
(3) Becomes unilateral

3. Clinical course of attacks
a. Frequency by decades
b. Variation of different attacks

4. Nausea
a. Early in life
b. Late in life

5. Emesis
a. Early in life
b. Late in life

6. Time of onset of symptoms
a. Chiefly upon arising
b. Morning
c. Afternoon

7. Nasal congestion
a. Precedes attack
b. With the pain
c. After headache

8. Psychic symptoms
a. Temporary amnesia
b. Visual hallucinations
c. Depression
d. Attacks of true psychosis
(1) Confusion
(2) Stupor, hallucinations, delusions
(3) Delirium

V. POST HEADACHE PHASE

1. Rhinorrhea
2. Polyuria
3. Exhaustion
4. Sleepiness
5. Edema
a. Where?
b. Grade?
6. Generalized soreness
7. Euphoria

VI. PREDISPOSING FACTORS

1. Menses
2. Emotional stress and suppression
3. Anger
4. Pregnancy
5. Constipation
6. Fatigue
a. Physical
b. Mental
7. Excessive use of the eyes
8. Food
a. Before examination
b. After clinical trial

VII. ASSOCIATED ALLERGY IN PATIENT
1. Hay fever
2. Asthma
3. Hives (not all cases)
4. Eczema (infantile or recurrent in adult)
5. Gastrointestinal disturbances (known to be due to food)
6. Purpura (?)
7. Arthritis (?)

VIII. FAMILY HISTORY
1. Headache
   a. Age of onset in different members
   b. Recurrence of attacks
   c. Frequency
2. Hay fever
3. Asthma
4. Eczema
   a. Infantile
   b. Recurrent in adult
   c. Other forms
5. Urticaria
6. Chronic stomach complaints
7. Epilepsy
8. Cancer
9. Tuberculosis
10. Hypertension
11. Obesity
12. Arthritis
13. Average weight
   a. Males
   b. Females
14. Average height
   a. Males
   b. Females

IX. CLASSIFICATION OF SYMPTOMS
1. Hemicrania
   a. Cortical features
   b. Noncortical
2. Bilateral pain
   a. Cortical features
   b. Noncortical
3. Frontal headaches secondary to nasal obstruction

For the purpose of comparative study cases have been grouped as follows: (1) The entire group studied; (2) those with complete relief on allergenic management; (3) patients with partial relief by this plan of therapy and in whom specific foods or inhalants could be demonstrated.

There is yet to be found any one feature of the history or symptomatology that indicates allergy as a factor in migraine. This is considered to be the most significant finding of the study. It may be interpreted as (a) that sensitization is not a *primary* factor, or (b) that it (allergy) exists in all cases, but our ability to detect and eliminate the offending fac-

tor is not such as to obtain the expected results, or (c) that migraine can be precipitated by many causes. A similar condition is found in some cases of urticaria (often wrongly called an allergic disease), there being many etiologic groups, one of which is allergy.

ANALYSIS OF THE SYMPTOMATOLOGY

Age of Onset.—Complete relief has been obtained regardless of when symptoms began, but the probability of aid is best if the onset was before puberty.

Frequency.—Whether attacks occurred less than or more than three times per month did not affect the benefit derived. They averaged over five times per month in those with complete relief. The prognosis for relief is best in patients with frequent irregular attacks.

Periodicity.—If attacks recur at definite intervals, i. e., fourteen to twenty-one days, or if they occur only at the menstrual period, allergenic therapy has little to offer.

Duration.—The period over which attacks have occurred, or the duration in each attack has no relation to the benefit obtained.

Cortical Features.—(Sensory, motor and vasomotor symptoms.) These have no apparent significance, being equal in all three groups. All forms except the ophthalmoplegic have been observed in the second and third groups. The presence of these phenomena is more important from the diagnostic standpoint than from that of therapeutic expectancy. These features have been produced repeatedly by deliberate feedings.

The Attack.—Neither the location, i. e., frontal, temporal, etc., nor the type of pain, i. e., unilateral or bilateral, has had any bearing on the ultimate improvement. Nasal symptoms occurred in a minority, and when present the average relief was less than in those without such symptoms. Facial pallor during attacks was associated with exceptionally good results.

Postmigrainous Stage.—Polyuria was a minor complaint; rhinorrhea was uncommon in the entire group studied. In patients with either symptom, the results were within the general average.

Predisposing Factors.—An increase of attacks at the menstrual period did not preclude marked benefit. It has been good in these patients, as it has been in those with an increase due to emotional stress or excessive use of the eyes.

Associated Allergy.—If migraine be an allergic disease, one would expect the greatest benefit in those with other allergy, but this has not been the case. While headache patients with asthma responded better than those with hay fever, neither group made as much improvement as did those without any other sensitization phenomena.

Family History.—Patients with neither allergy nor headache in the family were aided the most; those with a headache pedigree did better than the group with headache and allergy. However, the probability

that any benefit is to be obtained, is best in those cases with a positive family history.

Forms of Headache.—Whether attacks were the same in each instance or varied through all possible forms, did not influence the results nor does it have any prognostic value.

Food Relation.—Patients who knew before treatment that some food or foods would cause headache obtained the most benefit of all. This was the one finding of either the history or the symptomatology that appears to be of definite prognostic value.

Drug Therapy.—Ephedrine was tried in nearly all of the patients and was found to be of aid more often than any one other drug. However, in those patients where it was of value, the response to allergenic management was no better than the general average.

Complete Relief.—There were no features of the history or symptomatology of this group essentially different from the other two, except that neither periodicity (fourteen to twenty-one day intervals, etc.) nor ophthalmoplegic symptoms, or attacks only at the menstrual period were noted.

Recurrence.—The probability of allergy as a factor in any case of migraine is less likely to be aided by a consideration of the symptoms of the various attacks, except ophthalmoplegic, than by a study of other features, especially that of recurrence. The law of chance is definitely against one contacting an allergen at definite intervals over a period of time. It can and does happen, but a detailed history will solve those cases due to sensitization. Nor should we expect a food to be allergenic *only* at the menstrual period. For the most part, relief by food manipulation has been of aid in those instances where attacks recurred at irregular intervals.

Conclusions.—It is our opinion that one can estimate the probability of allergy as a factor in migraine more accurately by a study of the frequency and time interval of attacks, the age of onset, the diet and family history, than by any other clinical features of this disease. It appears that an allergic factor can be eliminated in those cases having (a) periodicity, i. e., fourteen to twenty-one days, etc., not explainable by the history; (b) attacks only at the menstrual period; and (c) headaches with ophthalmoplegic symptoms.

It is worthy of note that such a detailed analysis of a large series of cases fails to demonstrate any definite clinical features by which one can establish the diagnosis "allergic migraine." Therapeutic trial is the only means of diagnosing migraine due to allergy.

The analysis just presented could be used in support of the allergic theory of migraine, since nearly all types of migrainous symptoms have been relieved, and with the three exceptions noted, there is little difference between the unaided group and those entirely relieved. It would be just as logical, however, to contend on the basis of this same fact,

that allergy is not a primary specific factor. This re-emphasizes the fact that migraine is a clinical, not a pathologic entity, for which no one etiologic group alone can be held responsible. Thus one realizes the need as suggested by Riley[7] in 1932, of more and detailed study of both individuals and groups, before attempting to draw conclusions concerning any factor in migraine.

B. Studies of Individual Cases of Migraine Due to Food

Arguments in favor of the allergic theory of migraine must take into consideration the following questions: (a) Can the periodicity of attacks, i. e., symptoms for six to eight months, with an interval of months or years be explained on this basis? (b) What is the duration of sensitivity? (c) What are the clinical features and practical importance of a newly developing sensitization? (d) Can these patients build a tolerance to the specific foods or inhalants as is done in patients with asthma or hay fever? Answers to some of these questions are to be found in the following clinical record.

SPECIFICITY, DEVELOPMENT, DURATION, AND TRANSMUTATION OF FOOD SENSITIZATIONS IN A PATIENT WITH MIGRAINE HEADACHES

A physician, aged thirty-seven years, subject to recurrent sick headaches has recorded the following observations. There was a familial history of hay fever, asthma, hives, eczema, sick headaches and gastrointestinal allergy. When five years of age he suffered his first attack, it being severe enough that he remembers the one-sided pain and the duration. There were no other headaches until during his late "teens" (1914-1916). In 1918 he had an unusually severe hemicrania with scintillating scotomata and retrocular pain. Thereafter he continued to have occasional headaches, sometimes with vertigo, again without, until in February, 1924, when attacks became very severe for about one month, after which they practically ceased until the winter of 1928 when they recurred with similar symptoms as in 1924. At this time symptoms of perennial vasomotor rhinitis occurred and were alleviated by feather elimination. There were occasional headaches then until in the early part of 1931 when attacks occurred two or three times weekly and were accompanied with scintillating scotomata, paresthesias and often with hemianopia. These attacks were practically confined to the first two weeks of each month and were found to be due to eating apples and onions. It was also possible to explain the attacks in 1924 and those of 1928 on the basis of the diet history. On these three occasions large amounts of apples were taken in the diet during these periods. The following observations were made concerning the degree of sensitivity to apple. At first peeled apple could be taken without causing symptoms. Later on, any raw apple was found to induce an attack, but the cooked fruit could be used without causing difficulty. At this time he attempted to build a tolerance

to apple by eating graduated amounts. The result was that he experienced symptoms if either the raw or cooked apple was taken in the most minute amounts. Apple and onion were omitted then until in October, 1931, when clinical trial was made with both, apple, alone causing symptoms.

In November, 1931, he began to have a dull pain on one or the other side of the head each day. This began as a slight annoying dull pain and became increasingly severe over a period of ten days, at which time he developed a classical (for him) migraine. These symptoms were proved to be due to pecan. There were no further headaches then until in December, 1932, when following deliberate overeating he had an attack of migraine which was preceded by abdominal cramping and diarrhea. It was concluded after repeated food trials that this attack was not due to a specific food, but was provoked by overeating (indigestion). Directly thereafter, he tried apple and pecan and found that neither produced headache, but the former caused severe sneezing, lacrimation, rhinorrhea, and nasal blocking.

During the period that he was free of headaches he noted scintillating scotomata on many occasions and once suffered with quadrantic blindness in the left upper field of vision (homologous). This was not associated with any other symptom of headache. Shortly after the elimination of apple and onion in the spring of 1931 it was learned that cherries, corn and grapes would cause diffuse abdominal cramping which was followed by diarrhea and persistent pain in the right lower quadrant of the abdomen. These foods were eliminated with complete relief of distress. Several weeks later a clinical trial was made with grapes and urticaria was the only phenomenon observed. In February, 1932, he suddenly developed symptoms of perennial vasomotor rhinitis which had previously been aided by the elimination of feathers in 1928. After clinical trials were completed it was found that sneezing, rhinorrhea, and nasal blocking occurred when he ate the following foods: wheat, corn, oats, buckwheat, rice, barley, potato, sweet potato, beets, orange, egg, grapefruit, lemon, pineapple, watermelon, muskmelon, raw peaches, raw pears, peanuts, chocolate and apples.

From these observations it appears that cycles of headache can be due to periodic sensitization. The patient noting at least three instances (the winters of 1924, 1928, 1931) during which apples would induce headache. Food sensitization is apparently not permanent, since he is unable to produce headache at this time by eating apples, pecans, or onions, even though repeated attempts have been made. Third, we note transmutation of symptoms induced by food; in 1931 apple produced headache and corn induced diarrhea, in 1933 apple and corn both excite symptoms of vasomotor rhinitis. Grapes at one time caused diarrhea and a few weeks later produced urticaria and after an omission of several months were without any ill effect. It is quite probable that the previous cycles of migraine were due to variations in his reaction to foods. Had

he done nothing about his headaches it is quite likely that he should have continued with symptoms in cycles as before.

THE SPECIFICITY OF FOODS PRODUCING MIGRAINE ATTACKS

It has been considered correct to assign an allergic factor to those foods specific for attacks. That this procedure is open to question is indicated in the following clinical record. I treated a woman some months ago for sick headaches, relieving them entirely by the elimination of several foods. A short time later it was necessary to deny her another food. She finally consulted another physician who replaced these articles in her diet and instituted endocrine therapy (pituitary) with perfect results. Experience with this latter form of therapy warrants the prophecy that after a period of time she will not be relieved by it alone. The important feature of this case is the fact that complete relief was obtained by two different methods of treatment, thus raising the question of a primary specific effect of these foods for her migraine.

II. THE DIAGNOSIS OF AN "ALLERGIC STATUS" IN THE MIGRAINOUS INDIVIDUAL

The evaluation of this constitutional factor cannot be done by skin tests, family history, hereditary studies, or the occurrence of allergy in the migrainous patient, since they are only presumptive aids. While food elimination with consequent relief and subsequent reproduction of symptoms on ingestion denotes it is a causative factor, it does not indicate whether it be a primary or secondary cause, neither does it imply the mechanism of reaction, (i. e., allergic or toxic), and the latter is a very necessary antecedent to the diagnosis of atopy.

Those who contend that migraine is an allergic (atopic) disease must first prove that the true migrainous individual is an allergic one, and second, that the immunologic mechanism of symptom production is identical to that of the atopic diseases, i. e., hay fever and asthma. Until such studies have shown this to be the case, we cannot ascribe to the inclusion of migraine, *as a disease entity,* in the category of the allergic (atopic) diseases. On the other hand, the controversy concerning the classification of migraine as an allergic disease should not take precedence over the fact that allergic therapy is a decidedly successful procedure in many patients with recurrent headaches, familial in nature.

CONCLUSIONS AND SUMMARY

1. There are widely divergent views concerning the allergic factor in migraine.

2. An analysis of the history and symptomatology does not reveal any definite findings by which one can establish the diagnosis of migraine due to allergy. This can only be done by clinical trial. However, it is most probable in those patients with early onset, frequent, irregular attacks,

and a family history of headache according to the findings available at the time of this report.

3. The development, duration, clinical course, transmutation and specificity of food reactions have been reported in a patient with migraine.

4. The precipitation of migraine by various specific foods is not sufficient evidence to warrant the inclusion of it (migraine) in the category of the allergic (atopic) diseases. Necessary antecedents to this classification is the proof that the patient is an atopic individual and second, that the mechanism of symptom production is the same as in that of hay fever and asthma.

5. These statements in no way deny the importance of foods in certain cases, nor do they depreciate the study of their probable effect in any case of migraine, but they are intended to emphasize the need of conservatism in the interpretation of certain clinical observations and the necessity of detailed study of both individuals and groups of these patients before attempting an evaluation of allergy as a factor in migraine.

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927 ARGYLE BUILDING.

OBSERVATIONS ON THE INCIDENCE OF THE HYPERSENSITIVE STATE IN ONE HUNDRED CASES OF EPILEPSY

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THERE is considerable evidence at hand supporting the belief that certain structures of the central nervous system may act as atopic shock organs. Vaughan[1, 2] in 1922 and subsequently, suggested that some cases of migraine are due to meningeal irritation of hypersensitive origin. More recently Coca[3] has presented evidence that the retina may act as an atopic shock organ. In recent years the migrainal syndrome particularly has commanded the attention of students in the field of hypersensitivity. Numerous observers have claimed the existence of a close relationship between this condition and epilepsy. Buchanan[4] has called attention to the close relationship existing between these two conditions from the standpoint of heredity. As early as 1904 Spratling[5] suggested that individual susceptibility to certain foodstuffs must be considered as an etiologic factor in the attacks of some epileptic patients. Pagniez and Lieutaud[6] in 1919 noted changes in the white cell count in an epileptic patient after ingestion of chocolate and suggested that the hemoclastic crisis so produced, as well as the seizures which followed, were of anaphylactic nature. The sensitization factor in the etiology of epilepsy was called to attention by Welcher[7] in 1921 and in the same year by Thompson.[8] Ward[9] in 1922 definitely suggested protein sensitization as a cause of epilepsy, presenting reports of two cases of Bell, in which patients skin tests had been performed. Howell[10] in 1923 reported an intimate study of 14 epileptic children with results of skin testing. All except one were claimed to have been found sensitive to one or more foodstuffs, and some of them were sensitive to bacterial proteins. In 1923 Wallis and Nicol[11] with Craig reported results of skin tests with group food extracts and peptone on 122 patients with epilepsy, finding 46 giving positive reactions. In 1924 McCready and Ray[12] presented nine cases in which sensitivity to proteins was apparently a factor in the causation of convulsive disorders. In the same year Miller[13] presented a general summary of the evidence at hand at that time that idiopathic epilepsy is a sensitization disease. In 1927 Ward and Patterson[14] presented a detailed discussion of the subject with a review of the literature. They reported the results of cutaneous testing on 1000 epileptic patients and on 100 nonepileptic controls. In a group of 500 patients at the Craig Colony 37 per cent were found with positive skin reactions, and of 500 patients in the New Jersey State Village for Epileptics

56.8 per cent gave positive skin reactions; the control group showed only 8 per cent with positive skin reactions. In the same year Spangler[15] presented an analysis of 100 cases with regard to allergy. In his review, this author minimized the value of skin testing in epilepsy but stressed the value of food histories, claiming that with such histories, offending foods responsible for the attacks could be determined in some cases, and further stated that the ketogenic diet may owe its value to the accidental elimination of certain offending food proteins. In a later contribution this author stated that the observation of Tinel and Santanoise of the "existence of alternating periods of sensitivity and immunity" in their epileptic patients may have accounted for his previously reported unsatisfactory experience with skin tests to foods in epilepsy. Isolated cases of epilepsy due to foods have been reported by other observers.[17, 18, 19, 20]

However, opinion is not all in accord that protein sensitization is a factor of importance in the etiology of epilepsy. Many authors in discussing epilepsy entirely omit reference to the subject. Cohen and Lichtig[21] reported the absence of an abnormal incidence of epilepsy in the families of 250 patients with asthma, nor could they find a relationship of the protein reactions found in the only one of ten epileptic children who gave positive reactions, to the etiology of her seizures. Rackemann[22] found only a very low incidence of epilepsy in 3000 cases of suspected hypersensitivity. Talbot[23] in discussing the subject quoted the above two authors and made mention of contradictory evidence from observations in the Children's Clinic of the Massachusetts General Hospital, and summarized that "Evidence seems, therefore, to indicate that whatever relationship there appears to be between the two conditions is accidental and not of etiologic significance."

Opinion is, therefore, decidedly controversial concerning the factor of hypersensitiveness in the etiology of epilepsy. With an unusual opportunity at hand to investigate this question further, the present preliminary study was made. From the 1034 patients of the Abilene State Hospital, an institution for the treatment of epilepsy, 100 were selected for analysis. Our purpose was to determine, if possible, whether or not the incidence of the hypersensitive state is greater in this group of epileptic patients than in normal individuals. The criteria for the selection of the group to be studied were as follows: first, onset early in life, no case was included where symptoms begin after thirty years of age; second, absence of known organic or other etiologic basis for the attacks; third, absence of marked mental deterioration. There were 67 males and 33 females in the group. The oldest patient was fifty-eight years of age, the youngest eight years of age; the average was 26.3 years of age. The age of onset varied from infancy to thirty years, the average being 12.2 years. The frequency of attacks varied widely, but excluding six patients who had rather infrequent attacks, the seizures occurred once every ten days in the average patient.

The problem was first approached from the frequency of occurrence of

such accepted manifestations of hypersensitivity as hay fever and asthma in the antecedents, and in the patients themselves. A history of attacks of eczema, urticaria, migraine and epilepsy was also noted. We next sought to determine the presence of the hypersensitive state by the occurrence of demonstrable skin sensitivity in the patients, to representative inhalant and food atopens.

ANALYSIS OF ANTECEDENT AND PERSONAL HISTORIES

Questionnaires were mailed to the parents or close relatives, inquiring into the occurrence of hay fever, asthma, eczema, urticaria or hives, migraine or recurrent sick headaches, and epilepsy in the patients, and their antecedents. The patients themselves were also questioned directly concerning the above conditions. It is admitted that such histories are subject to considerable error, but for the most part replies both from the patients and from their relatives were intelligent and presumably fairly accurate.

Antecedent Histories.—In 42 per cent of the histories there was obtained no record of any of the above named conditions in the antecedents. A history of hay fever was obtained in 7 per cent and of asthma in 16 per cent; both diseases occurring in the antecedents in 2 per cent of the cases. There was thus found a history of one or both of these conditions in the antecedents in 21 per cent. In 14 per cent a history of eczema or urticaria was found. Recurrent sick headaches occurred in 42 per cent. Epilepsy occurred in 22 per cent. In these tabulations the separate occurrence of these conditions in the paternal, maternal or bilateral history was not noted. The incidence of a positive history of hay fever or asthma in the antecedents of these patients (21 per cent) is strikingly higher than that given by Spain and Cooke[24] for normal individuals; these investigators finding only 7 per cent of a group of 115 normal persons with a positive antecedent history of these conditions. However, this percentage is much lower than that found by them in a series of 462 selected cases of hay fever and asthma; their study showing 58 per cent positive antecedent histories in this group. Cooke and Vander Veer[25] in another series of 504 cases of hay fever and asthma had reported 48.4 per cent of positive antecedent histories, and Adkinson,[26] 50 per cent of 191 cases of asthma. Thus, it may be inferred from a consideration of the above figures that the incidence of the hypersensitive state in the antecedents as shown by the occurrence of these two conditions alone, is higher in our series of epileptic patients than in normal individuals, but lower than that found in hay fever and asthma patients. We feel that the history of eczema and urticaria is of much less significance in determining the hypersensitive state, due to errors in diagnosis by the layman and the less definite rôle played by hypersensitivity in many of these cases. Of even less significance is the history of recurrent sick headaches, due to the probable inclusion of headaches not of the migrainal type, and the questionable part hypersensitivity plays in many of these cases. The occurrence of epilepsy in the antecedents in 22

per cent of this series supports the opinion of many observers of a familial factor in the etiology of this condition.

Personal Histories.—In this series very little evidence of the hypersensitive state in epilepsy is suggested by the coexistence of such known manifestations of hypersensitivity as hay fever and asthma. No patient gave a personal history of hay fever, nor could such history be obtained from physicians in charge of their respective wards. Only one patient gave a history of asthma; this being corroborated by observation in the hospital. Six of the patients gave a history of urticaria, but in only one of these was the condition observed while in the hospital. The history of eczema was not obtained in any case. The incidence of migrainal headaches was impossible to determine due to frequent headaches associated with the seizures.

CUTANEOUS REACTIONS

The investigation of the hypersensitive state was next approached from the standpoint of cutaneous reactions. We acknowledge that the presence or absence of demonstrable skin sensitivity is at best an inaccurate index of the hypersensitive state, as is illustrated in the unsatisfactory demonstration of reagins in many accepted hypersensitive conditions. Nevertheless, cutaneous testing constitutes an integral part of the study of the hypersensitive etiology of most conditions in this field. Realizing the great difficulty of testing such a series to all known atopens, the following atopens were selected as representative possible offenders in this section; pollens: mountain cedar, mesquite tree, representative pollens from the grass family, including Bermuda, timothy and maize, a mixture of pollens from the order Chenopodiales including, lamb's-quarters, Russian thistle, spiny amaranth, careless weed, pigweed, and western water hemp, a mixture of three ragweeds, giant ragweed, short ragweed and western ragweed. Other inhalants included: orris root, horse epithelium (horse serum also included), cat epithelium, dog epithelium, goat epithelium, rabbit epithelium, wool (sheep), cottonseed, kapokseed, flaxseed, house dust, tobacco, feathers (chicken, duck, and goose), and pyrethrum. Foods included: milk, egg, beef, lamb, pork, chicken, catfish, wheat, corn, rice, rye, oats, barley, white potato, green pea, celery, lima bean, spinach, tomato, carrot, peanut, watermelon, banana, orange, coffee, mustard, and black pepper. Other atopens not routinely but frequently used were: turnip, cucumber, cauliflower, lettuce, cabbage, rhubarb, onion, asparagus, cantaloup, pineapple, coconut, raisin, grape, strawberry, prune, peach, apple, and vanilla. These extracts were prepared according to Coca's[27] technic, the nitrogen content of many of them being determined by the Kjeldahl method. All extracts used had been shown by clinical tests to be nonirritating. All of the extracts of the pollens and other inhalants and a large percentage of the foods were known to have been potent, as shown by positive reactions in clinically sensitive individuals. The intradermal method

was used in testing the entire group. Those reactions considered positive or questionable were further investigated by the method of local passive transfer in proved receptive skins.

RESULTS OF CUTANEOUS TESTING

In 70 per cent of the series no positive or questionable reactions were demonstrated. In the remaining 30 per cent positive or questionable reactions were found. In 19 of these 30 cases specific atopic reagins could not be demonstrated in the serum by the method of local passive transfer. In nine of this latter group some degree of reaction was obtained in a majority of the sites tested, suggesting at once a nonspecific reaction in a hyperirritable skin. Of the remaining ten cases, from one to nine sites gave questionable or definite reaction to an orderless group of both inhalants and foods. In none of the above 19 cases was there any corroborating clinical evidence of the hypersensitive state, and in only three instances was there a history of hay fever or asthma in the antecedents. In the remaining 11 cases specific atopic reagins were demonstrated in the sera by the method of local passive transfer. A more detailed discussion of this group is warranted.

Case No. 20. Male, aged thirty-seven years. No personal history of accepted hypersensitive manifestations. His mother was subject to eczema. The epileptic attacks began at the age of eight years and occurred with an average frequency of one attack every three days. By the method of local passive transfer specific reagins were demonstrated to: horse epithelium, cottonseed and chocolate.

Case No. 25. Male, aged seventeen years. No personal history of accepted hypersensitive manifestations. An uncle was subject to epilepsy and a grandmother to recurrent sick headaches. Epileptic attacks began at the age of twelve years and occurred with an average frequency of one attack weekly. By the method of local passive transfer a specific reagin was demonstrated to mountain cedar pollen.

Case No. 26. Female, aged twenty-four years. No personal or antecedent history of accepted hypersensitive manifestations. Epileptic attacks began at the age of sixteen years and occurred with an average frequency of two attacks daily. By the method of local passive transfer specific reagins were demonstrated to: mesquite tree pollen, pork and barley.

Case No. 41. Male, aged twenty-six years. No personal or antecedent history of accepted hypersensitive manifestations. Two sisters were subject to frequent headaches. Epileptic attacks began at the age of thirteen years and occurred with an average frequency of one attack monthly. By the method of local passive transfer specific reagins were demonstrated to: mountain cedar pollen, mesquite tree pollen, timothy grass pollen, corn, green pea and lima bean.

Case No. 44. Male, aged thirty-two years. No personal history of accepted hypersensitive manifestations. A grandmother was subject to re-

current headaches. Epileptic attacks began at the age of nineteen years and occurred with an average frequency of one attack daily. By the method of local passive transfer specific reagins were demonstrated to: cat epithelium, cottonseed, kapokseed, lamb, wheat, green pea and coffee. This patient on two occasions had epileptic seizures while being tested.

Case No. 46. Male, aged thirty-nine years. He had had frequent attacks of urticaria since childhood. No antecedent history of accepted hypersensitive manifestations. Epileptic attacks began at the age of twenty-one years and occurred with an average frequency of one attack every ten days. By the method of local passive transfer specific reagins were demonstrated to: mesquite tree pollen, mixed chenopod pollens, cottonseed, kapokseed, wheat, oats, barley, tomato and coffee. A severe attack of urticaria developed on two occasions while being tested.

Case No. 83. Female, aged twenty-four years. No personal history of accepted hypersensitive manifestations. An uncle was subject to epilepsy. Epileptic attacks began at the age of twenty-two years and occurred with an average frequency of one attack every two days. By the method of local passive transfer specific reagins were demonstrated to: egg, tomato, rice, mustard and peanut.

Case No. 86. Male, aged thirty-two years. No personal or antecedent history of accepted hypersensitive manifestations. Epileptic attacks began at the age of thirty years and occurred with an average frequency of one attack every two weeks. By the method of local passive transfer specific reagins were demonstrated to: spinach, barley, and corn.

Case No. 87. Male, aged twenty-two years. There was a personal history of bronchial asthma beginning at the age of ten years. No history of accepted hypersensitive manifestations in the antecedents. Epileptic attacks began at the age of eighteen years and occurred with an average frequency of one attack every two weeks. By the method of local passive transfer specific reagins were demonstrated to: mountain cedar pollen, mesquite tree pollen, milk, beef, lamb, pork, rice, green pea, spinach, carrot and coffee.

Case No. 90. Male, aged eighteen years. No personal or antecedent history of accepted hypersensitive manifestations. Epileptic attacks began at the age of two years and occurred with an average frequency of one attack daily. By the method of local passive transfer specific reagins were demonstrated to: corn, rice, barley, white potato, green pea and peanut.

Case No. 92. Male, aged thirty years. No personal or antecedent history of accepted hypersensitive manifestations. Epileptic attacks began at the age of twenty-six years and occurred with an average frequency of one attack weekly. By the method of local passive transfer specific reagins were demonstrated to beef and lamb.

Considering the antecedent history of the above cases it will be noted that in no case was there a record of hay fever or asthma. In one case a history of eczema occurred, in two, migraine, and in two, epilepsy.

It must be taken into consideration that in several of the above enumerated cases an adequate explanation of the presence of specific reagins can be found in other clinical phenomena presented by the patient. The reactions in Case No. 87 can be fully explained on the basis of a bronchial asthma of twelve years' duration. In Case No. 46 the history of repeated urticarial attacks offers a possible explanation of the reactions, particularly in view of the fact that the intradermal testing on two occasions precipitated a severe urticarial rash. In Case No. 25 specific reagins were demonstrated to mountain cedar pollen only. Since the seizures in this patient are not seasonal, it is extremely unlikely that this atopen is related to their etiology. However, in the remaining eight cases there is no adequate explanation for the presence of the specific atopic reagins demonstrated in their sera.

DISCUSSION

From the foregoing report it is at once observed that the incidence of hypersensitivity, as determined by the occurrence of hay fever and asthma alone, in the antecedents (21 per cent), is definitely higher than that accepted for normal individuals. The occurrence of demonstrable atopic reagins in the sera of patients in this series (11 per cent) is also definitely higher than that reported in normal persons. While these findings do not approach the percentages found in known hypersensitive conditions such as hay fever and asthma, they are of sufficient variance from the accepted normals to be considered of some significance. In the antecedents of patients of this series the incidence of hay fever and asthma, as well as of other less definitely accepted hypersensitive conditions, is much lower than that reported by Spangler[15] in an analysis of a similar number of cases of epilepsy. Ward and Patterson[14] and Wallis and Nicol,[11] in their reports, make no mention of the incidence of hypersensitivity in the antecedents of their patients. The percentage of positive cutaneous reactions obtained by Wallis and Nicol (37.7 per cent) as well as by Ward and Patterson (average 47.9 per cent) is much higher than that obtained in our series. It may deserve mention that approximately 59 per cent of the positive cutaneous reactions recorded by Ward and Patterson are tabulated as plus-minus reactions. The results of the cutaneous tests obtained by these observers were not subjected to critical verification by the method of local passive transfer, without which some suspicion must be held in mind of nonspecific reactions. The inference made by Wallis and Nicol, and also by Spangler (quoting Tinel and Santanoise), that skin reactions may vary greatly or entirely disappear in certain phases of the epileptic cycle is open to some question. The variability of skin reactions has been the subject of considerable controversy. Our experience with other hypersensitive manifestations has led us to believe that demonstrable specific reagins when present are not subject to such variations. Failure to demonstrate their presence does not, of course, exclude the existence of the hypersensitive state.

If it may be assumed that an abnormally high incidence of the hypersensitive state in a considerable group signifies a possible etiologic relationship, the findings as noted above would indicate a hypersensitive factor in some cases of epilepsy. Results of treatment should yield additional information, and investigations in line of treatment are now being conducted and will be recorded in a subsequent report.

SUMMARY

1. The literature on the subject is briefly reviewed. Opinion expressed by various observers is controversial regarding the relationship of hypersensitivity and epilepsy.

2. In a study of 100 selected cases of epilepsy the occurrence of hypersensitive manifestations in the antecedents is found higher than that in normal individuals, but lower than that reported in such accepted hypersensitive conditions as hay fever and asthma.

3. The low incidence of hay fever, asthma and eczema in the patients of this series is noted.

4. The occurrence of demonstrable atopic reagins in the sera of 11 per cent of this series is somewhat higher than expected in normal individuals but is much lower than that reported in such accepted hypersensitive conditions as hay fever and asthma.

5. Our analysis indicates a greater incidence of the hypersensitive state, in this series of epileptic patients, as determined by the occurrence of hypersensitive manifestations in the antecedents, and by demonstrable atopic reagins, than in normal individuals.

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LOCALIZED PURPURA ASSOCIATED WITH MALARIA

Case Report

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A REVIEW of the literature on purpura reveals that many and varied causes have been assigned, such as typhoid fever, pregnancy, tuberculosis, drugs, allergy (food), and malaria. The assumption is that purpura is a vasomotor manifestation of a toxemia or of various toxemias. Macleod[1] mentions malaria as a cause. Stelwagon[2] states that Tyrrell, in 1876, considered malarial toxemia an important factor. Eyermann and Strauss,[3] reporting a case of urticaria, referred extensively to the literature, and suggested that "an urticaria occurring as the result of infestation with malarial parasites may be fairly held to be an allergic phenomenon." Alexander and Eyermann[4] in 1927 reported three cases of purpura associated with allergy. Later they reported six similar cases and were able to demonstrate that in each case the lesions were caused by particular foods.[5] Barthelme[6] reported a case of purpura due to the ingestion of wheat or of egg yolk.

It has been my privilege for more than a year to study a case of recurrent localized purpura. Observations over this period suggest a local sensitization, analogous to the phenomenon every allergist has seen, of urticarial wheals appearing at the site of former injections of an allergen when another injection is made, or particularly when the patient is exposed to the allergenic substance in nature.

Mrs. J. H. S. was referred to me by her husband, a physician, in January, 1932, for allergic study. The complaint was a recurrent, itching, painful rash on her hands. The first attack had been in the fall of 1931. Attacks were occurring about once a month, and each succeeding one had been quite similar to the first, with no perceptible variation in severity, distribution, or duration. With one exception, they started between 11 and 1 o'clock at night. One began at 8 P.M. The following syndrome did not vary. The first symptom was tingling of lips and fingers. In a very few minutes itching of the fingers became very intense, and affected areas were acutely reddened. The parts involved were the dorsal surfaces of the fingers, the distal phalanx of the right thumb, and small areas on the dorsum of the left hand, the left hypothenar eminence, the volar surface of the left forearm, and the right wrist immediately proximal to the thumb. The itching persisted for two days and was not alleviated by x-ray or local applications, including 10 per cent cocaine solution. By the second day, the first intense redness changed to deep purple, and parts were quite painful. In five or six days the dead epidermis was

separated from the tender dermis by a small amount of brownish fluid. After a few days the affected tissues became normal, except for a brawny discoloration which persisted between attacks.

The family history is positive for allergy, one brother being an asthmatic under treatment. The patient herself had had rare attacks suggestive of angioneurotic edema of the lips.

The patient had been a normal healthy child. The only past illness considered of significance was malaria in 1926. A basal metabolic test had shown a rate of minus 28, and she had been taking thyroid for some months without change in the recurrence of the rash.

Repeated blood studies revealed a leucopenia (3,000 to 4,500). Red cells were about 4,000,000. Gastric analysis showed normal acidity of the gastric contents. Skin tests to allergens were negative. In June, many malarial parasites were found in the blood cells. Treatment was instituted at once. On the second day of quinine therapy, an abortive attack occurred. Quinine was discontinued on July 28. No further attacks occurred until the first week in September, at which time malaria again was found. The leucopenia persisted. The patient was again given quinine, this time for a longer period (until November 22). No attack has occurred since the one in early September. Frequent blood examinations are being made, and although the leucopenia persists, no malaria has been found to date (March 29, 1933).

The significant features of this case are: (1) the family history is positive for allergy; (2) the definite localization of the purpura; (3) the existence of malarial infestation without constitutional symptoms; and, (4) the association of the lesion with malaria and the apparent effect of quinine therapy upon it.

NOTE.—Another attack of the rash similar in onset to all previous attacks has occurred since this paper was written. Quinine therapy was started immediately. An abortive course was run, without the stage of deepest discoloration and sloughing being reached.

I wish to thank Dr. A. F. Pirnique, Pathologist at the University of Arkansas, for many blood studies and other laboratory work done on this case.

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SENSITIZATIONS OF ECZEMATOUS TYPE: TEN SELECTED CASES ILLUSTRATING SOME USES OF THE PATCH TEST*

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SINCE the patch test was first employed in this country (Markley[1]) and was introduced as a routine measure of investigation in the practice of Wise and Sulzberger,[2] many interesting cases and causes of dermatitis eczematosa have been brought to light. We are selecting for report but a few of the many cases which have come under our observation in the last four years. These few are chosen each for some specific reason or reasons, which will be mentioned in the discussion of the particular case.

In addition to these more specific reasons, we report these cases because we believe they illustrate some matters of general interest in connection with the question of eczematous idiosyncrasy—such as, for instance, the practical value of the patch test, the necessity for a flexibility of procedure and of painstaking, incessant and repeated questioning of the patient. In addition to this, we believe that these cases show that the causes of eczematous dermatitis are practically infinite in number, that no substance is beyond the pale of suspicion, and that a logical approach, exact investigation of the patient's milieu at home and at work, provided the clinical appearance indicates such a procedure, sometimes lead to results of great benefit in heretofore apparently hopeless cases.

The patch test, which was introduced by J. Jadassohn,[3] developed by Bloch,[4] and which did not come into general use in this country until it was systematically employed by Sulzberger and Wise,[2] has in recent years proved of incalculable value in the search of the etiology in so-called contact eczemas. Moreover, the use of the patch test is a valuable adjunct in dermatologic practice in enabling the physician to avoid causing a severe or widespread irritation through the application of supposedly curative medicaments.

Unfortunately, as is well shown in the cases we report, most drugs and especially those most used in dermatology may be causes of eczematous dermatitis (white ammoniated mercury, butesin picrate, picric acid, quinine, resorcin, bichloride of mercury, etc.). A patch test with the therapeutic agent to be employed and a short wait (twenty-four to forty-eight hours) before the general application, can frequently prevent untoward reactions, unpleasant to the patient and disastrous to the reputation of the physician. These untoward results have made it a dictum that the older and more experienced the dermatologist, the weaker the concentrations of the therapeutic agents he employs. With the nonexistence of hypersensi-

*Based on a paper read on January 12, 1933, before the Dermatological Society of the New York Post Graduate Hospital of Columbia University.

tiveness once established in a particular case through negative patch tests, it is usually safe to employ even high concentrations of the agent, and therefore even the oldest dermatologist may make use of the strongest applications, with their frequently correspondingly greater therapeutic effect.

It is interesting to note in connection with the above statement that many of the cases listed are due to drugs which have been employed by the patient to combat preexisting conditions, often of less severity than the dermatitis venenata which ensued.

CASE 1.—*Sensitization from the use of a new proprietary local anesthetic.* Patient, A. P., suffered from a perianal eczema and pruritus of the scrotum and groin. In the course of treatment a 1 per cent nupercaine ointment (Ciba) was prescribed to counteract the intense itching. Two weeks after the first application, there was marked edema, erythema and scaling of the scrotum and penis. Ten days after this, a severe bullous erythema multiforme-like eruption appeared all over the body, with 25-cent-piece-sized bullae on dorsa of hands and on groins (due to nupercaine ?). Through an error, nupercaine was used again, two weeks later, because of the severe and persistent pruritus ani. Two days after this second application, a vesicular, edematous and erythematous dermatitis appeared at the site of application. There were maddening itch crises, persisting even weeks after the actual dermatitis had disappeared.

Patch tests with nupercaine 1 per cent, cocain 1 per cent, novocain 1 per cent, anesthesin 1 per cent, butyn 1 per cent, and butesin 1 per cent were performed.

The test with nupercaine was strongly positive (4 plus, graded according to Bloch), and all others were negative.

This case demonstrates that the new anesthetic nupercaine can be the cause of eczematous sensitiveness.[12] Eczematous sensitivity to the older local anesthetics is well known. (See James,[5] procain; Sulzberger and Wise,[6] butesin.) The results of our patch test showed that sensitivity to one anesthetic is not necessarily connected with sensitivity to others, and that this method may be used in selecting the one to be employed in a given case.

Furthermore, we should like to point out certain characteristics of sensitivity which may be more or less peculiar to sensitization with anesthetics, or at least most frequently encountered in cases sensitive to chemicals with local anesthetic action. The period of time between the first application of nupercaine and the appearance of the first eruption was fourteen days. This is apparently the time during which sensitization developed. The period elapsing between the second application and the appearance of the second eruption was only twenty-four hours, and the positive patch took the same length of time to develop.

We must, therefore, distinguish: (1) a period of incubation, during which sensitivity develops, which is approximately of the same duration

and probably analogous to the manifestations in serum sensitization, experimental primrose and arsphenamine sensitizations, etc.; and (2) a period of reaction time, which usually remains constant and is generally twenty-four hours to seventy-two hours.

It is also noteworthy that excruciating crises of itching persisted for many weeks after cessation of the application of the remedy and healing of the dermatitis. This seems to be a frequent occurrence and quite typical of sensitivity to local anesthetics, and may be, in some way, connected with their particular affinity for nerve structures. All of these points have been alluded to and discussed in detail by Sulzberger and Wise[6] in connection with butesin picrate sensitization.

Cases 2 and 3.—*Sensitizations to substances not employed by the patient, but by other persons in the patient's environment.*

Case 2.—Eczematous dermatitis due to a new proprietary ointment (mazon ointment). Mrs. J. R. presented a diffuse erythematous and edematous, sharply demarcated dermatitis of the entire left arm and a scaling and acutely reddened dermatitis of the right hand.

Questioning elicited no history of contact with suspicious substances and only the fact that the patient had washed her daughter's clothes shortly before the appearance of the dermatitis. Further close questioning revealed that the daughter had had a ringworm infection and had used mazon ointment. Patch tests with mazon ointment showed a markedly positive reaction (Bloch—grade 4) after twenty-four hours on Mrs. J. R., the mother, who had not actually employed the ointment—while the daughter, who was not sensitive, had used the ointment with impunity.

Case 3.—Dermatitis due to calmitol. Patient D. N., when first seen, had an acute eczematous eruption of the left hand and wrist, of the sides of the neck and of the inguinal regions, scrotum and genitals.

As no other cause of the dermatitis venenata could be discovered and as the patient's wife also came to us for treatment for pruritus vulvae, we inquired as to the remedies she had previously employed to control her itching. One of these, calmitol, gave a strongly positive patch test reaction in her husband, while the wife was not hypersensitive. Upon discontinuance of the use of calmitol on the part of the wife, the husband's dermatitis disappeared and has not recurred. (Observation period—one and one-half years.)

Cases 4 and 5.—*Hatband leather dermatitis; illustrating the occurrence of familial eczematous sensitivity.*

Case 4.—Patient A. P., the father, suffered from a persistent, recurrent papular and pruritic eruption of the forehead, as well as from a seborrhea sicca of the scalp and seborrheic dermatitis-like eruption of the face. Before consulting us, he had been treated elsewhere during seventeen years as a case of papular seborrhea of the forehead.

After many unsuccessful attempts with other substances, patch tests

with leather from hatbands were found strongly positive; and the site of the tests was still severely inflamed when observed four and one-half weeks after the application. We ordered elimination of all leather hatbands (the patient had to have all his hats lined with silk bands) and, to date, i. e., since one and a half years, there has been no recurrence.

CASE 5.—Dermatophytosis and dermatophytid plus dermatitis due to leather and dye.* R. P., the son of A. P. (Case 4), first consulted us in January, 1930. He had been suffering from an acute eczematous eruption on the hands and feet, recurrent during seven years. This had defied all treatment, even at the hands of five of this country's most reputed dermatologists who had employed all manner of therapy, including full courses of x-ray.

When first examined, the patient had very little scaling between the toes and a scaly, infiltrated and erythemato-vesicular eruption on the dorsa and sides of the feet. The eruption reached up the ankles to about the height of the tops of a pair of low shoes. There was a severe vesicular eruption on all the fingers, as well as on the palms and dorsa of both hands.

We diagnosed the condition as a dermatophytosis and dermatophytid and began desensitizing the patient with trichophytin. On May 3, 1930, the patient was discharged cured. He was completely desensitized to trichophytin, showing no reaction to a concentration which had caused a very severe local reaction and a flare-up of the hand lesions upon the first injection in January.

The hand lesions were cured at this time and have remained cured, without recurrence to date, with the exception of one small eczematous patch in January, 1931. One injection of trichophytin sufficed to cure this. At this time, the reaction to trichophytin was very slightly positive, but since this test and to date, repeated trichophytin tests have proved negative and there has been no recurrence of a dermatophytid. (Three years' observation.)

In contradistinction to this, the patient had recurrent eczematous eruptions of the sides and dorsa of both feet. Because of the persistence of the foot lesions in spite of complete trichophytin desensitization; and because of the peculiar demarcation and localization of the dermatitis on the dorsa of the feet, we decided, on Feb. 15, 1931, to test the patient with the leathers of his various shoes. Black shoes of a certain manufacture gave positive eczematous reactions to patch tests, whereas brown shoes and certain makes of black shoes were negative. The patient's skin was also tested with paraphenylendiamine (2 per cent in vaseline), which gave a markedly positive reaction. The patient was instructed to avoid all shoes except those which had not caused a dermatitis on testing; and rigidly to eschew the wearing of dyed or colored socks. The dermatitis of the feet

*This case was included among those mentioned in the report of Sulzberger and Wise on therapeutic trichophytin desensitizations, read before the Section of Dermatology, American Medical Association, June 10, 1931.[7]

then disappeared, and there has been no recurrence of either foot or hand lesions to date. (Observation—nine months. Last summer was the first in eight years during which the patient was free from foot lesions.)

(It is interesting to note that upon later questioning and with a knowledge of his father's case, the patient recalled that some years previously he, too, had apparently been sensitive to leather. He had had an eruption of the forehead due to hatbands, on the wrists due to boxing gloves; and had even been obliged to have his wrist watch attached with a metal band, as the leather one had caused a severe irritation.)

We believe that this case presents several noteworthy features: first, the curing of the dermatophytid of the hands through trichophytin desensitization (compare reference 7); second, the lasting desensitization achieved (three years' duration); third, the sensitization to dyed leather, following dermatitis apparently due to fungi.

The last observation illustrated some points which it is well to bear in mind and which were recently discussed by White and Taub,[8] and by Osborne and Putnam.[9]

Sensitizations and dermatitis due to external substances may precede and also initiate fungous disease, either (a) through affording portals of entry for subsequent fungous infection; or (b) they may lead to multiple or polyvalent sensitization and eventually embrace even hypersensitivity to fungous products, thereby causing patients to react with dermatitis to the previously innocuous fungi which may have been present.

In addition to this—as we believe may have been the sequence in Case 5—a sensitization and dermatitis due to fungi can bring, in its wake, sensitizations to other substances, including those which belong to the group of exogenous, eczematogenous allergens. For example, in our case it is conceivable that a dermatitis of the feet, due to fungi, prepared the way (injury, maceration, erosions, friction, portals of entry, etc.) for sensitization to leather or dyes.

A third possibility to be considered is that the presence of a dermatophytid or a dermatitis venenata shows that the particular patient, at that particular time, possesses an unfortunate susceptibility to eczematous sensitization in general and is, therefore, more prone to multiple sensitization. This, of course, obviates the necessity for assuming that the first or preceding sensitizations and dermatitides are in the relationship of cause and effect to the subsequent ones.

This is the opinion now held in regard to multiple sensitizations in such conditions as hay fever, in which the patients are frequently hypersensitive to a number of chemically unrelated allergens, derived from various grasses, pollens, etc.

It is necessary to bear in mind all of these possibilities, and they become of great practical importance in the consideration of industrial dermatoses and, more particularly, in their relation to compensation.

Furthermore, the consideration of Cases 4 and 5 brings to light a very

unusual familial occurrence of eczematous hypersensitivity of the real dermatitis eczematosa type. Frequent as are the familial occurrences of hay fever, asthma, neurodermites, infantile eczema, etc., the familial occurrence of the true dermatitis venenata type of eruption is, in our experience, extremely rare. We believe that the cases cited merit consideration from this viewpoint, even though one disregard the even more remarkable fact that sensitivity to one and the same substance seems to have existed in both father and son at one time, both having been sensitive to leather as prepared for hatbands. (Compare Stauffer.[10])

Cases 6, 7, and 8.—*Cosmetic eruptions.*

CASE 6.—Dermatitis due to face powder. Mrs. S. G. was first seen on Jan. 20, 1931, presenting a diffuse, red and scaly eruption on the entire face and neck. The normal lines of the skin were accentuated in the affected area and there was mild itching. The patient stated that the skin condition had been present for the past two months. About a month prior to the appearance of the dermatitis she had started to use a new face powder—Chanel's "Une Idee."

We performed patch tests on the patient's back with various cosmetics and other substances. They were all negative, with the exception of the site of the "Une Idee" powder. At the twenty-four-hour reading, this showed a Bloch 1 plus reaction (erythema). At subsequent readings, there was no increase in the intensity of the reaction.

We then performed a patch test with the same powder on the patient's neck in the so-called V-area, that is, just above the manubrium sterni. A twenty-four-hour reading of this test site demonstrated a Bloch *3 plus* reaction, that is, intense erythema and vesicles.

Elimination of the face powder and substitution of one of our own prescriptions brought about a cure, and there has been no recurrence to date.

CASE 7.—Dermatitis due to face powder. Miss S. H. was first seen on February 21, 1931, presenting a dermatitis of the mid-portions of the face, with marked erythema, scaling and slight infiltration. The nose was practically denuded of epidermis and the eyelids were swollen. There was intense itching.

According to the patient's statement, the eruption had commenced suddenly ten days before. Six weeks previous to consulting us, she had started using a new face powder—Chanel's "Une Idee."

A patch test was made on the V of the neck and on the back with this face powder. A seventy-two-hour reading revealed the fact that while the patch test on the back was negative, the one on the front of the neck showed a circumscribed, definitely erythematous reaction.

Cessation of the use of the offending powder brought about a permanent cure.

CASE 8.—Dermatitis due to hand cream. Mrs. C. S. first consulted us because of an eczematous dermatitis of the hands and wrists, on October 24, 1932. This dermatitis was then of two weeks' duration.

Patch tests revealed the fact that the patient was hypersensitive to a Paquin hand cream. All other tests were negative. The patient had been using this cream on her hands without ill effects for over two years. We could find no cause for the apparently sudden onset of the sensitization.

These three cases again illustrate the fact with which every dermatologist is familiar, namely, that various cosmetics may cause dermatitis in sensitized individuals. The report of the two cases of face powder dermatitis is of interest because, as far as we know, no sensitizations to this particular powder have been reported. By a curious coincidence, within one month we chanced to see two patients who were hypersensitive to the same powder.

The analysis of the results of the patch tests in cases 6 and 7 shows, first, that a given person's skin may not be equally sensitive to a substance in every area at a given time; and, second, that in both cases the sensitivity of the V-area of the neck was greater than that of the back and corresponded in its sensitivity with the skin of the face.

It would seem the most logical explanation for the similarity in reaction of the face and the V of the neck to assume that these two areas had been exposed to more intimate and frequent contact with the offending allergen than the back. However, there are other possible explanations, including viz.: (1) The sensitization taking place on the face, gradually and progressively spreads from the primarily sensitized area until the whole skin has eventually become hypersensitive. Therefore, in testing early cases of sensitization, one may find that only the parts adjacent to the areas which first became sensitized will react. This fact has support both in experimental sensitizations and in the observations on spontaneous sensitizations in human beings.[3, 10] (2) Both the face and the neck were generally uncovered in our two patients (young women), and the exposure to the elements may have, in some way, contributed to make these areas sensitive in contrast to the covered area on the back. (3) There may be fundamental anatomic or functional relationships existing between the skin of the face and that of the neck, which cause these areas to respond in similar manner. This last is borne out in some degree by the predilection of certain dermatoses for these two areas (seborrheic dermatitis, syringocystadenomas, lupus erythematosus, etc.).

The fact remains, whatever its explanation, that we have found the similarity of reaction between the face and the V of the neck in still other cases of dermatitis venenata of the face. *We believe, therefore, the V of the neck to be admirably qualified to be a testing ground in cases of dermatitis of the face.**

The last three cases cited also bring out the fact that the time elapsing between the initial contact with the offending allergen and the beginning

*In the last week we have seen yet another case of dermatitis of the face and eyelids due, apparently, to face powder. Patch tests with all manner of cosmetics, including the powder, were negative on the patient's arms. The patch test with face powder was strongly positive on the V-area of the neck.

of the sensitization is a variable with large fluctuations. (Case 6—one month; Case 7—thirty-two days; Case 8—two years.)

We must, therefore, establish three steps in the chronology of every case of eczematous sensitization: (1) *Period of refractoriness to sensitization*—ending with the *beginning* of the process of sensitization. During this period, the patient has been coming into contact with the allergen, apparently without becoming sensitized. This period is extremely variable in length and seems to have a range between zero and an indefinite number of years. (2) *Period of incubation of sensitivity*, corresponding to the incubation period of infectious diseases and of such sensitizations as serum sickness, experimental arsphenamine sensitizations, etc. During this period, the process of sensitization is progressing, but the disease has not yet become manifest. This period is usually nine to fourteen days, in the cases which we have observed. (Case 1 in this article, and cases of butesin sensitization.[6]) (3) *Period of reaction time.* That is, the period elapsing between the contact of the causative agent with the skin of an already hypersensitive individual and the clinical appearance of the reaction. This is often constant in a given case and generally varies from case to case, from approximately eighteen hours to seventy-two hours.

The knowledge of the extremes in variation of the period of refractoriness to sensitization makes one realize that substances which have been in contact with the skin without apparently damaging it for years, may suddenly cause sensitization and dermatitis for no ascertainable reason. Our questioning of the patients must, therefore, include not only substances which have been recently introduced into their lives, but also substances which they have been in contact with for years with apparent impunity.

Case 9.—*Dermatitis due to a thimble.** This case is of more practical than theoretical interest. The patient, Mrs. G. E., a milliner, was sent to us by an insurance company on March 21, 1932. She had punctured her finger with a needle on August 18, 1931, and had not worked since August 27, 1931. Since the injury, the insurance company had been paying her compensation, doctors' fees, medicaments, etc. They referred the patient to us for opinion and suggested either *removal* of the nail or even of the end phalanx of the middle finger, or deep incision. The case had been variously diagnosed as: (1) erysipeloid; (2) acrodermatitis continua pustulosa of Hallopeau; (3) chronic lymphangitis; (4) dermatitis repens; (5) bullous lupus erythematosus; (6) streptococcus infection; (7) tinea, etc. The therapy, including intravenous injections of gold salts and local x-ray treatments, had been of no avail in preventing repeated recurrences.

On first examination, the patient presented redness and swelling of the distal and second phalanx of the middle finger of the right hand. She stated that a few days previously the entire end phalanx had been covered by a huge blister.

*This case was presented by Dr. Coombs at the New York Dermatological Society on Feb. 23, 1932.[11]

On March 22, we performed patch tests with the scrapings from two different makes of a white composition thimble which she had been using (imitation white celluloid or rubber). It was only after much persuasion that the patient admitted the very infrequent use of these thimbles during her period of illness. The tests were applied on various parts of the body to determine possible localized sensitivities. After twenty-four hours, they were strongly positive at all sites. Controls with these materials were negative on normal individuals. Avoidance of contact with such thimbles (substitution of a silver thimble over a silk glove finger-tip) brought about a cure, and there has been no recurrence to date. (Observation—eight months.)

This case is cited to emphasize the practical importance and the possible economic advantages to be gained through use of the patch test. It is also an example of the possibility of sensitization after trauma (pin-prick followed by sensitization to material of thimble).

CASE 10.—*Drug eruption.*[6] Patient E. T., a young woman of twenty-two years, was first seen in 1930. She had a severe, highly inflamed vesicular dermatitis of the scalp, face, eyelids and neck; and a vesiculo-bullous dermatitis of the hands and forearms. She had been using a hair tonic containing quinine, advertised as a dandruff cure.

Patch tests with this and with quinine hydrochloride were strongly positive, and the patient was cautioned against the use of quinine in any form. The patient remained free of eruption for more than a year. In April, 1932, she again came for relief. She now had an erythematous and scaly dermatitis, resembling an acute dermatitis exfoliativa of the entire body and a vesicular and weeping dermatitis of the previously affected areas (face, scalp, hands and forearms). While the generalized exfoliating dermatitis improved rapidly and the skin of the body was almost normal in a week, the vesicular eczema took over three weeks to clear up. There was no history of external contact with quinine, but the patient had taken a bromoquinine laxative tablet about three hours before the appearance of the second eruption. Patch tests with quinine were again strongly positive, while those with bromine were negative.

This case serves as an example of a fact which has long been known, but which perhaps needs more general recognition. A dermatitis of eczematous type can be caused by contact with a substance of exogenous origin or of hematogenous distribution. Provided a sufficient quantity of unaltered allergen reaches the shock tissue (in this case, the epidermis), that shock tissue reacts in its specific and characteristic fashion, in this case an eczematous, vesicular and scaling dermatitis.

We consider it unnecessary to discuss this phenomenon here, but refer to previous publications citing and discussing cases of this kind.[3, 4, 6] Besides demonstrating the fact that hematogenous allergen and allergen coming into contact with the skin from the outside may cause the same clinical picture, Case 10 again presents evidence that a patient's skin need not be

equally sensitive in all its parts at a given time. The skin of the scalp, face, hands and forearms was evidently much more hypersensitive than the remainder of the body. The skin of these areas reacted with a more or less persistent bullous and vesicular dermatitis, while the remaining skin presented a relatively ephemeral scaly erythema. It is worthy of attention that *the areas which had been previously affected by external contact were precisely those that were more highly hypersensitive.* This fact is of extreme importance. In patch testing occupational dermatoses the sites of previous eruptions must be tested before a substance can be excluded from suspicion.[10] In reference to this observation, we can only refer to what has been said in Cases 6 and 7 concerning the origin of skin hypersensitivity and the possibility of its gradual centrifugal spread from the areas of first contact with the sensitizing agent. Further speculation as to the connection between the first external contact dermatitis and the possibly resultant higher degree of sensitivity of the first sensitized areas would be interesting, but would lead us too far afield.

The points touched upon in this communication are too many and too varied to admit of a brief recapitulation. It seems to us, however, that these cases are all in some way enlightening. We hope that the descriptions and the discussions of each case are self-explanatory and will help either to record a new observation or to emphasize an old fact concerning the patch test and eczematous dermatitis.

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CLINICAL URTICARIA AND HAY FEVER. AN UNUSUAL SYMPTOM COMPLEX*

A Case Report

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THE following case report of H. C. is interesting in that it presents a clinical urticaria associated with hay fever. The literature does not contain the record of a similar case nor have we ever observed one in our Clinic.

Brown[1] reported a case of urticaria and dermatitis caused by grass pollens. The patient was sensitive to tests with pollen extract but did not have hay fever. Taub and White[2] also reported a case of urticaria caused by grasses. There was no hay fever. The skin test with pollen extract was positive. The patient did not do well under treatment with pollen extract but improved when not in contact with the offending grasses.

H. C., aged twenty-eight years, seen first on August 30, 1929. He gave a history of attacks of autumnal hay fever for three seasons. The symptoms were the usual ones of sneezing and itching of the eyes, but in 1929 for the first time he was troubled with general urticaria. The symptoms mentioned began a few days before his first visit.

Skin tests with ragweed extract gave marked reactions to dilutions containing 0.0001 and 0.001 mg. nitrogen per cubic centimeter. On account of the numerous lesions over his chest and back he was tested with the foods habitually eaten. Orange and lamb gave marked reactions.

The patient was instructed to avoid these foods, and in addition received daily injections of ragweed extract. Both urticaria and hay fever improved a great deal, and the impression at that time was that the cessation of urticaria was probably due to the abstinence from the aforementioned foods.

In the years 1930 and 1931 preseasonal treatment was given, and during both seasons the patient had no urticarial lesions, although suffering slight hay fever. Lamb and orange were eaten during this time.

In 1932 preseasonal injections were not given, and the patient appeared first on September 2. Hay fever symptoms began on August 23 and urticaria on the following day. The skin lesion was general and severe. Cutaneous tests gave marked reactions to the dilutions previously mentioned. Tests with lamb and orange were negative. Patch test with ragweed oil did not produce wheal or dermatitis.

Injections of ragweed extract were given daily for four successive days,

*From the Department of Allergy, Roosevelt Hospital.

then every second day. Improvement was noted after the fourth injection, and in a week the urticaria had largely disappeared. This patient had never had urticaria except with hay fever.

Since patients with hay fever regularly exhibit such an exquisite degree of skin sensitiveness to pollen extracts, the wonder has been that hay fever patients did not regularly have clinical urticaria as a part of the symptom complex of hay fever. The absence of urticaria, however, has been adequately explained by the demonstration of Cohen et al.[3] that the absorption capacity of the nasal mucosa in allergic individuals is very poor in comparison with nonallergic individuals. The case presented seems to be a rare exception to the rule.

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ECZEMATOUS DERMATITIS DUE TO EXPOSURE TO CHLORAL*

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CHLORAL hydrate (chloral) was discovered by Liebig in 1832 and introduced as a hypnotic by Liebreich in 1869. It occurs as colorless, transparent, slowly volatile crystals, that are easily soluble in water, and in other solvents. Chemically it is the hydrate of trichloraldehyde, $Cl_3C\text{-}CH(OH)_2$. Its effects soon became almost common knowledge with the lay public. Addiction to the use of this drug was recently reported as gaining ground in India.[1]

Reports of skin eruptions produced by the internal administration of chloral were comparatively infrequent, even at the time of its widest use. Those described were almost always of the erythema group, i. e., scarlatiniform, morbiliform, urticarial, erythematovesicular and the petecheal types.[2] The most recent report of a chloral rash that could be located in the literature was by Gregor,[3] in 1907. The eruption described was of a generalized maculopapular type, scarlatiniform in appearance. Although chloral had been replaced to some extent by synthetics whose depressing action on the circulation was less marked, it was still used extensively. It may be that chloral rashes were then less often encountered, due to the use of less heroic dosages or perhaps it was no longer considered of any importance to report such cases.

In addition to its internal sedative action, chloral was also being used on occasions as a local antineuralgic and antipruritic agent, in the form of an ointment, liniment, etc. Eruptions following the external use of the remedy were still more uncommon than when prescribed internally, in spite of the fact that chloral was considered as a local vesicant and also a caustic. Labadie-Lagrave and Degny[4] reported two cases where a macular and papular eruption followed the use of chloral in vaseline. Morrow[2] quoted Cantani who said that the external application of chloral produced erythema and vesicles. Morrow also quoted Ritter who found that powdered chloral on adhesive plaster when applied to the skin caused denudation after ten minutes. Peyraud[5] found that 0.02 grams of chloral in a gum resin vehicle applied for eighteen hours to one square centimeter of skin surface regularly caused vesication. In solutions it was said to excite a caustic action.

We have located only one case, reported by Kirn,[6] of an eczema that

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became generalized following the repeated internal administration of chloral, mostly by rectum. We thought it would be of interest to report a patient who evidently became sensitized to chloral through frequent contact with this drug, and as a result developed an eczematous dermatitis that recurred after subsequent exposures to this substance. As far as we could determine, sensitization to chloral produced in this way with the development of eczematous lesions had not as yet been mentioned in the literature.

CASE REPORT

Mr. J. S., was fifty-five years of age, born in Russia and a druggist by profession. He was in excellent health until about five years ago when he had to have his right kidney removed for a hypernephroma. There was no sign of a recurrence of the neoplasm to date. The patient gave no personal history of allergy, but he said his brother had been subject to hay fever and asthma for many years, and one sister had died in an asthmatic attack.

At various times during the past twenty-six years, the patient was subject to an eczema of the hands. He came under observation June 26, 1930, presenting an acute erythematous and papulovesicular and scaly eruption, that involved the dorsum and palmar aspect of the hands and fingers. No other eruption was present on the body, excepting between the toes, where some fine scales were present. A microscopic examination of the vesicles on the hands and from the scales between the toes did not reveal any fungi. Nevertheless he was told to apply a 2 per cent tincture of mercurochrome to the affected toes, as it was suspected that he might have a fungus infection in this area with a dermatophytid of the hands. The latter was treated with a mild crude coal tar ointment and also with a few fractional x-ray treatments. The condition cleared up nicely.

He reappeared four months later with the skin of his face dusky red in color and swollen. The hands again showed an acute eczematous eruption that now involved the extensor surfaces of the forearms. This time an external irritant was suspected, and when questioned along this line, he gave us a clue that finally led to the detection of the cause of his skin trouble. For years he had been compounding at least four or five prescriptions daily containing chloral as an ingredient, as one of the physicians in his neighborhood was rather liberal in ordering it. The patient doubted that there was any connection between the handling of chloral and his skin outbreak.

Patch Tests to Determine Sensitization and Subsequent Clinical History.—By means of patch tests, suitable aqueous solutions of chloral and some of the other drugs that he was likely to handle were applied to the normal skin of the back of the trunk and to the flexor aspects of the forearms. All were left in place for twenty-four hours and then removed. The following substances were chosen for the tests:

1 Per cent quinine hydrochloride
10 Per cent chloral hydrate
1 Per cent bichloride of mercury
10 Per cent sodium salicylate
1 Per cent capsicum
1 Per cent resorcin
1 Per cent atropine
1 Per cent belladonna
1 Per cent cantharides
Powdered ipecac

There was only a slight erythema where the bichloride of mercury and sodium salicylate solution had been placed, but there was a marked blistering and denudation with surrounding edema and redness where the chloral hydrate had been applied. All the other substances gave no visible skin reaction, although observed for several weeks. There was no aggravation of the preexisting eczematous areas.

In view of the positive skin reactions to chloral, that persisted for almost one week, he was advised not to come in contact with chloral hydrate, to avoid any further outbreaks. His eruption cleared up under the usual local treatment.

He returned on April 17, 1931, with a recurrence of the eruption on his face, hands and forearms. He had continued to handle the drug but was "very careful" with it. His eruption was of a few days' duration and presumably followed a lapse in whatever precautionary measures he took in compounding prescriptions containing chloral.

Another series of patch tests was performed, using the normal skin on the flexor surfaces of the arms, this time with the following substances:

Lanolin
Palmolive soap
Cocoa butter
1 Per cent salicylic acid solution
Ephedrine powder
10 Per cent chloral hydrate solution

All the patch tests gave a negative reading on the skin twenty-four hours later, excepting where the chloral hydrate had been applied. This was again strongly positive, (blistering, denudation with surrounding redness and edema).

On June 9, 1931, one of us (E. W. A.), was called in to see him by his family physician. The dermatitis had reappeared on his face and hands. He had been a little careless again in handling the chloral. One of the skin lesions on his left hand had become infected, and a lymphangitis had developed affecting his left arm and forearm. Several large pustular lesions on his fingers had been opened by his physician. A num-

ber of indurations were developing along the lymphatics of the forearm and arm. There was no adenopathy. The infection subsided after ten days under dressings of Burow's solution (1:8) and rest of the affected extremity. The dermatitis lasted only a few days. The peculiar tendency to secondary infection in chloral rashes had been previously reported by Geill,[7] but it evidently occurs in other drug rashes of an eczematous nature.

He was entirely free of any further skin eruptions until January 11, 1932, when another recurrence developed. The eczematous lesions again began on the back of his hands and also appeared on his face. He was not seen during this outbreak, but this eruption also followed the careless handling of chloral. He was advised to try desensitization treatment, or to let some one else compound chloral prescriptions.

He was seen recently (March 5, 1933). He had no recurrences of his skin eruption for over one year. He said that he personally filled no more prescriptions containing chloral. He had an assistant make up a stock solution and handle the drug when necessary. Patch tests were used this time with 1, 2, 5, and 10 per cent dilutions of chloral hydrate and 1 per cent solution of bichloride of mercury. They were removed after twenty-four hours, and all areas except where the mercury had been applied showed marked degrees of edematous erythema with central vesiculation and denudation, varying with the dilution used. The reaction was most marked where the 10 per cent chloral hydrate patch test had been applied. We interpret these reactions as showing that our patient was still sensitized to chloral and the reason that he was free of any relapses during the past year was that by having a stock solution of this drug made (chloral hydrate itself was somewhat volatile), and having some one else handle it, he had reduced to a minimum all chances of coming in contact with this drug.

COMMENTS

We patch tested other patients with various dermatoses that appeared at the New York Post-Graduate Skin Clinic, using the same dilutions of chloral hydrate mentioned above. One patient (woman with eczematous eruption) gave a positive skin reaction, and only with the two stronger solutions of chloral. The areas tested presented a moderate degree of erythema and vesiculation, but no visible edema or denudation. We could not elicit any exposure to chloral in this subject. She did not return to be tested further with other irritants. Four other patients with eczematous lesions that were tested gave negative reactions to the various dilutions of chloral. One patient with urticaria and four others with acne vulgaris also gave negative tests. We also applied the various solutions of chloral on ourselves as normal controls and obtained no reaction whatever, even after forty-eight hours' contact.

If a single positive patch test with 5 to 10 per cent solutions of chloral

occurred in a small series of cases, it may be argued that a larger series would reveal other eczematous patients with a similar result, and hence such patch tests were not of a specific nature. In the patient we were reporting, simultaneous skin tests were carried out with other well known irritants like mercury, capsicum and cantharides, etc., and the skin failed to react with any of these except the chloral hydrate; the existence, therefore, of a specific hypersensitiveness to chloral had to be considered. A recent retest in our patient with weaker dilutions of chloral also gave strongly positive reactions, and further emphasized the specificity of the test. This together with the history of almost daily contact with chloral hydrate led us to assume that our patient had finally become sensitized to this substance and was now manifesting this sensitization by eczematous lesions whenever he was exposed to this drug. This assumption was further supported because his eruption had not recurred since he meticulously avoided exposure to chloral. Finally the most careful investigation could not elicit any other cause for the eruption. The patient was reluctant to take a test dose of chloral by mouth, even in the dilutions generally employed for desensitization. No passive transfer experiments were attempted.

On purely clinical ground the dusky erythema of the face and the eczematous lesions of the hands and arms, recurring each time with the handling of the drug, aside from the positive patch test, also favored the belief that chloral was the offending agent in our patient.

SUMMARY AND CONCLUSIONS

Reports of skin eruptions from the internal administration of chloral were infrequent, although it was widely used at one time. Those eruptions that had been reported were of the erythema group; scarlatiniform, urticarial, erythematovesicular and petecheal in type. An eczematous dermatitis from chloral was quite unusual; only one such reference was found.

Our patient, a druggist, became sensitized to chloral by frequent contact with it and finally became so vulnerable that the mere presence of this substance caused the outbreak of an eruption.

The type of skin lesions in our patient aside from the premonitory dusky erythema of the face, was an eczematous dermatitis of the hands and forearms and later the face. At one time a secondary skin infection occurred, a not unusual phenomenon in chloral rashes.

One to 10 per cent chloral hydrate solutions applied for twenty-four hours as patch tests caused a varying but marked degree of vesiculation and denudation with surrounding inflammatory edema of the tested area of the skin in our patient, while some other irritant drugs caused no visible local skin reactions.

A small series of cases with various skin diseases were tested with 1, 2, 5, and 10 per cent solutions of chloral hydrate, and with a single excep-

tion all showed negative reactions with the patch test. The exception was one of five eczematous patients who gave a positive reaction only with the 5 and 10 per cent solutions of chloral. This reaction was of a moderate vesicular nature and was nowhere so severe as that produced by a 1 per cent dilution in our sensitized patient.

The repeated outbreaks of the eczematous dermatitis with premonitory dusky erythema of the face following exposure to chloral, the freedom from such lesions when he was more than ordinarily careful to avoid contact with this substance and the positive patch test to chloral and not to some other irritant drugs, bespeak a specific sensitization to chloral with cutaneous lesions produced by this substance.

Such lesions produced in this particular manner have not as yet been reported as due to chloral.

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Department of Reviews and Abstracts

Selected Abstracts

Free Iodine in the Treatment of Vasomotor Rhinitis and the Symptom Complex of Sneezing and Nasal Hydrorrhea—Preliminary Report. Levine, M.: Laryngoscope **43**: 39, 1933.

Free iodine is thought to have some effect upon edema, which is the underlying lesion of vasomotor rhinitis, common cold, and hay fever. Pharmacologically, it has been established that iodine is eliminated in part by the mucous membrane of the upper respiratory tract, upon which it has a definite stimulating action. Because it has been found to be beneficial in cases of hydrorrhea it would appear that its influence is principally upon water metabolism.

Twenty cases of pure vasomotor rhinitis have been treated with a 5 per cent aqueous sodium iodide solution containing traces of free iodine. This was given in 1 c.c. doses subcutaneously. Injections were administered every two or three days until the symptoms completely subsided. As a rule, about six injections were required; as many as ten in more obstinate cases. In all instances, relief was obtained after two or more injections.

Cases of common cold were likewise treated; and, although results were gratifying, they were not so successful as in cases of vasomotor rhinitis. Laryngitis is a contraindication to treatment.

Studies on a Urinary Proteose. II. Skin Reactions and Therapeutic Applications in Hay Fever. Darley, W., and Whitehead, R. W.: Ann. Int. Med. **6**: 389, 1932.

A series of hay fever patients treated with proteose during the spring and summer of 1931 is reported.

Proteose was prepared according to the method of Oriel and Barber. Intradermal injections of 0.05 c.c. of proteose solutions were made down the volar surface of the forearm, and a positive reaction was a typical wheal with pseudopods developing within five to ten minutes. These reactions occasionally became so intense that the scratch method of testing was used, the material applied being N/10 sodium hydroxide-proteose solution with a N/10 sodium hydroxide as a control.

The initial dosage for desensitization was arrived at by selecting the dilution the next below that which gave the least positive intradermal reaction. The first dose was usually 0.05 c.c. subcutaneously. Injections were given at from three to four day intervals, and the dose was gradually increased or decreased as indicated by the patient's clinical progress. Thirteen cases were treated: 11 were of the early type of hay fever, and 2 of the late type. Of these 13 cases, 5 secured complete relief, 3 almost complete relief, and 5 partial relief.

The theories of the mechanism of desensitization are discussed.

Alimentary Anaphylaxis. Haritanis, A.: Presse Medicale **41**: 119, 1933.

A report is given of a case of alimentary anaphylaxis, unusual in that it presented none of the classical symptoms associated with the condition. The patient complained of a fever of about 38° with no sweats and no chills, which appeared in the afternoon and disappeared toward midnight, leaving the patient exhausted. This fever had persisted for three months and had resisted quinine treatment and treatment for typhoid and paratyphoid fever. Diet had been restricted to milk and a meat bouillon. Such was the condition when the patient was seen by the author. Examination showed a good general condition. There were no unusual findings except for the liver, which was enlarged and upon palpation was slightly painful. The patient having spent some considerable time in Russia and in Egypt, it was considered possible that the condition might be due to amoebae and accordingly treatment was instituted, which, however, gave no results. Antisyphilitic treatment was then given with no results. A leucocyte count, showing a relatively low number about an hour after the noon meal, led the author to consider the possibility of a digestive anaphylactic crisis. It was then remembered that the patient had complained of an erythema, periodic and fleeting, accompanied by a pruritus, and that he had noted that he found himself improved on days when in traveling he had been forced to limit his meals to watermelon. The patient was immediately put upon a liquid diet. The next day, for the first time in four months, the fever did not rise above 37°. The same diet was continued for another twenty-four hours without rise in temperature. Fruit juices and vegetable bouillon were successfully added to the diet. Further dietary experimentation showed that albumin was largely the offending element. Skin tests to peptone, milk and butter gave positive reactions. On an albumin-free diet the patient experienced a complete cessation of fever. After twenty days of such treatment the patient was fed a light albuminous meal and the fever recurred. Convinced that the case was one of alimentary anaphylaxis, desensitization was attempted with good results. The liver returned to nearly normal size and to date there have been no more attacks of fever.

A Second Case of Gastrointestinal Allergy Due to Insulin. Williams, J. R.: J. A. M. A. **100**: 658, 1933.

A woman aged fifty-two years had taken insulin for diabetes constantly for six years. In September, 1931, she began to have cramps followed by frequent bowel movements. Two months later, she noticed a slight edema of the upper eyelids. This occurred almost daily without accountable cause and despite treatment. Meanwhile the intestinal symptoms increased. Up to this time, the patient had been using insulin of pork origin, but through an inadvertence was given an insulin derived from beef. With this treatment, the cramps and diarrhea immediately ceased. Skin tests for insulin sensitivity thus revealed a marked reaction to pork insulin which persisted for twenty-four hours. During this time the intestinal symptoms reappeared. They were later reproduced by the administration of pork insulin. (The beef insulin gave no positive reaction.)

This is the second case of insulin allergy reported by the author.

"Quotientin," a New Combination Remedy in Bronchial Asthma. Gutmann, M. J.: Therapie der Gegenwart **73**: 430, 1932.

A difficulty encountered in treating asthma with adrenalin is that repeated doses of adrenalin tend to create a calcium deficiency in the blood. "Quotientin" is suggested as a new therapeutic agent. The preparation is of an adrenalin-like character, being, however, clearly differentiated from pure adrenalin and from ephedrin and ephetonin, and lying about midway between these two preparations. After injection, the calcium measure rises appreciably from the fourth hour until it comes to the highest point between the sixth and the fifteenth hour. If originally, the calcium content is low, the effect is particularly good. The calcium measure sinks rapidly so that the quotient becomes normal.

Quotientin was used upon about 120 allergic patients. The reaction was somewhat slower than that obtained with adrenalin but more continuous. In several cases longer periods of freedom from symptoms were obtained.

The effect upon asthmatic attacks is obtained for the most part from within two to five minutes and lasts for several hours. In severe cases, injection must be repeated after a short time to secure full results. The after-effects of Quotientin are much the same as those of adrenalin: quickened heart beat, trembling, pallor, etc., all of which symptoms last but for a short time.

Quotientin gave good results in hay fever cases not previously treated. It is not recommended for use in cases where the patients are very old people or children under three years of age.